A STUDY ON SERUM LIPID PROFILE AND SUBCLINICAL ATHEROSCLEROSIS IN RHEUMATOID ARTHRITIS

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INTRODUCTION

Rheumatoid Arthritis is the commonest form of chronic inflammatory joint disease. It is a symmetrical, non suppurative polyarticular disease unique to modern man.[1] Rheumatoid arthritis affects the synovial joints, but it is not confined to them and the many visceral manifestations have led to the classification of RA as a systemic disorder of immunological mechanism.[1]

Rheumatoid arthritis is associated with increased morbidity and mortality because of cardiovascular disease , independent of traditional risk factors.[15] Cardiovascular disease due to accelerated atherosclerosis is a leading cause of mortality in rheumatoid arthritis (RA). Endothelial dysfunction often precedes manifest atherosclerosis. Both traditional risk factors and inflammation-associated factors are involved in RA-associated atherosclerosis.

The contribution of inflammation to atherogenesis is supported by epidemiological evidence on the independent predictive value of inflammatory markers for subclinical and clinical atherosclerosis and for associated CV events. However, the impact of lipids on CV risk in the chronic autoimmune inflammatory setting of RA is unclear and the literature on lipid profile in patients with RA is contradictory. A number of studies

have demonstrated either a proatherogenic or a favourable lipid profile in RA. Growing evidence suggests that patients with active untreated RA have reduced total cholesterol (TC), low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol. The conflicting results can be attributed to confounding by indication and, possibly, to the effect of inflammation and treatment. Comprehensive analyses of trends in lipids both before and after RA incidence are lacking and the exact impact of RA onset on lipids is unknown.

Among imaging techniques, the early determination of common carotid intima-media thickness (ccIMT), flow-mediated vasodilation (FMD), and nitroglycerine-mediated vasodilation (NMD) may be useful to determine atherosclerosis and endothelial dysfunction.

The early diagnosis of endothelial dysfunction and atherosclerosis, active immunosuppressive treatment, the use of drugs that control atherosclerosis, changes in sedentary lifestyle, and the close follow-up of RA patients may help to minimize cardiovascular risk in these individuals. Preventing atherosclerosis and its progression remains a central goal in medicine.[13]

REVIEW OF LITERATURE

DEFINITIONS

RHEUMATOID ARTHRITIS

Rheumatoid arthritis is a chronic systemic inflammatory disease of undetermined etiology involving primarily the synovial membranes and articular structures of multiple joints. The disease is often progressive and results in pain, stiffness, and swelling of joints. In late stages, deformity and ankylosis develop. Rheumatoid arthritis can also cause significant extra-articular manifestations most probably related to systemic inflammation.[19]

PATHOPHYSIOLOGY

The genetic predisposition and the environmental factors, importantly infections play a major role in the causation of RA. The class II molecule particularly HLA- DR4 is associated with 70% of RA patients. The susceptibility to RA is associated with the third hypervariable region of the DR β chains from aminoacids 70 through 74. Deficient galactosylation of the immunoglobulin G might also be a risk factor for the development of RA. The primary targets of inflammation are synovial membranes and articular structures. Other organs are affected as well. Inflammation, proliferation, and degeneration typify synovial membrane involvement. Joint deformities and disability result from the erosion and destruction of synovial membranes and articular surfaces.[19]

Factors associated with rheumatoid arthritis include the possibility of infectious triggers, genetic predisposition, and autoimmune response. $CD4^+$ T cells stimulate the immune cascade leading to cytokine production such as tumor necrosis factor alpha (TNF-a) and interleukin-1.[19]

EPIDEMIOLOGY

Rheumatoid arthritis occurs throughout the world and in all ethnic groups. Its prevalence is approximately 1% of the population. ; women are affected approximately three times more than men. The prevalence increases with age but the sex difference diminish in old age. The onset is more frequent during the fourth and fifth decade of life, with 80% of all patients developing the disease between 35 and 50 years of age.[20]

CLINICAL FEATURES[25]

The clinical manifestations include articular and extra articular features. The articular manifestation may have an insidious onset in 55-65 % of patients, acute onset in 8-15% of patients and subacute in 15-20% of patients. The unusual pattern of onset may be adult onset Still's disease or polymyalgia rheumatic type. The joints most commonly involved first are metacarpophalangeal joints, proximal interphalangeal joints, metatarsophalangeal joints and wrists. The large joints become symptomatic after the small joints .

The extra articular manifestation includes subcutaneous nodules, episcleritis, scleritis, myositis, vasculitis, pulmonary manifestations in the form of pleurisy, interstitial fibrosis, nodular lung disease, bronchiolitis, pulmonary hypertension and small airways disease. Cardiac complications include pericarditis, myocarditis, endocardial inflammation, conduction defects, coronary arteritis, granulomatous arteritis or valvular disease.

DIAGNOSIS

1987 ACR Criteria for the Classification of Acute Arthritis of Rheumatoid Arthritis [25]

For classification purposes, a patient is said to have RA if he or she has satisfied at least 4 of the following 7 criteria. Criteria 1 through 4 must have been present for at least 6 weeks. Patients with 2 clinical diagnoses are not excluded.

1. Morning stiffness: Morning stiffness in and around the joints, lasting at least 1 hour before maximal improvement.
2. Arthritis of 3 or more joint areas: At least 3 joint areas simultaneously have had soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician; the 14 possible joint areas are right or left proximal interphalangeal (PIP)joints, metacarpophalangeal (MCP)

joints, wrist, elbow, knee, ankle, and metatarsophalangeal (MPT) joints.

3. Arthritis of hand joints: At least one area swollen (as defined above) in a wrist, MCP or PIP joint.
4. Symmetric arthritis: Simultaneous involvement of the same joint areas (see 2 above) on both sides of the body (bilateral involvement of PIPs, MCPs, or MTPs is acceptable without absolute symmetry).
5. Rheumatoid nodules: Subcutaneous nodules, over bony prominences, or extensor surfaces, or in juxta-articular regions, observed by a physician.
6. Serum rheumatoid factor: Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in <5% of normal control subjects.
7. Radiographic changes: Radiographic changes typical of RA on posteroanterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized to or most marked adjacent to the involved joints(osteoarthritis changes alone do not qualify)

Various inflammatory disorders of remote organ systems may be present and may contribute to the presenting problem. Organ systems that may be affected include the following:

- Cardiac - Carditis, pericarditis
- Pulmonary - Pleuritis, intrapulmonary nodules, interstitial fibrosis
- Hepatic – Hepatitis
- Ocular -Scleritis, episcleritis, dryness of the eyes
- Vascular – Vasculitis
- Skin - Subcutaneous nodules, ulcers.

LABORATORY STUDIES[19]

- Complete blood count (CBC) indicates the presence of anemia in approximately 80% of patients with rheumatoid arthritis (RA).
- The anemia is normocytic and normochromic.
- Thrombocytosis may be present.
- Erythrocyte sedimentation rate (ESR) is elevated in approximately 90% of patients with rheumatoid arthritis.
- Serum RF result is positive in approximately 70% of patients with rheumatoid arthritis. Antinuclear antibodies (ANA) are present in approximately 30% of patients with rheumatoid arthritis.
- Anti cyclic citrullinated antibody test is the latest addition to the list of

laboratory investigations. It may be positive in 60% of seronegative RA if second generation ELISA kit is used.

TREATMENT[19,24,26,30]

Treatment of rheumatoid arthritis comprises of **non pharmacological** and **pharmacological** therapies. It should have comprehensive regime directed towards treating the basic disease and the complications. Non drug therapy includes patient education, counseling and rehabilitative measures that that focus on pain control, patient adherence, rest, joint protection principles and exercise therapy.

Drug therapy includes analgesics, nonsteroidal anti-inflammatory drugs, corticosteroids either intra articular or systemic.

Current recommendations have become more aggressive in that, for all but minor disease, the use of DMARDs and/or biologic response modifiers or combination drug therapy earlier in the disease course is recommended in order to effectively slow or halt ongoing tissue damage.

The American College of Rheumatology established recommendations for the use of nonbiologic and biologic DMARDS in 2008. These guidelines are broken down by disease severity and by duration of disease presence at less than 6 months, 6 months to 24 months, or greater

than 24 months. The use of nonbiologic DMARDS is recommended early in the management (<6 months) of patients even with low disease activity and no features of poor prognosis. The use of combination DMARD therapy is phased in early and the further consideration of biologic DMARDS is recommended early if there are signs of high disease activity or features of poor prognosis.

Nonbiologic DMRDs include methotrexate , glucocorticoids, leflunomide , sulfasalazine, cyclophosphamide, hydroxy chloroquine, gold injections, d-penicillamine, minocycline , azathioprine &cyclosporine.

Biologic DMARDs include etanercept , adalimumab , abatacept, efalizumab, infliximab , rituximab , and certolizumab.

Systemic steroids are usually used as low dose daily therapy or high dose short course therapy as for drug induced thrombocytopenia, mononeuritis multiplex and interstitial lung disease, coronary arteritis. It can be used as a principal therapy during pregnancy when needed. The drugs used in the combination triple drug therapy are methotrexate, hydroxychloroquine and sulphasalazine.

Other drugs like leflunomide, cyclosporine, azathioprine, D-penicillamine and gold salts are used either alone or in

combination when the conventional DMARD combination therapy fails. The TNF α receptor antagonist Etanercept is a fusion protein of the soluble portion of the human TNF p75 chain of the receptor and the Fc portion of the human Ig G1 is used in patients who fail to respond to first line drugs and is shown to have higher improvement at ACR 20,50,70 responses. Infliximab, a chimeric monoclonal antibody has also been shown to reduce the clinical signs and symptoms along with slowing the radiological progression. Adalimumab is a fully humanized monoclonal antibody against TNF. Another drug is abatacept, a fusion protein of CTLA4 with IgG. Rituximab, an anti CD 20 B cell depleting agent have shown to have favorable results on the clinical as well as radiological progression of the disease. **Statins** were found to have beneficial effects in RA. Drugs which are under trial include p38 MAP kinase inhibitor, anit B cell stimulator (BLyS) and other anti cytokine therapies.

COMPLICATIONS[19]

- **Felty syndrome** is a triad of RA, neutropenia, and splenomegaly. Patients with Felty syndrome are prone to serious bacterial infections that result in higher rates of morbidity and mortality than for other patients with RA. This requires prompt diagnosis and initiation of antibiotic therapy.

- **Ruptured Baker cysts** are often confused with deep vein thrombosis (DVT). Baker cysts often occur fairly early in the course of the disease, with pain, edema, and inflammation in the posterior knee and calf. The diagnosis is best made with ultrasonography. Treatment includes rest, elevation, needle puncture of the calf, knee joint aspiration, and referral.
- **Carpal tunnel syndrome** (median nerve compression neuropathy) is evidenced by pain and/or paresthesias in the median nerve distribution of the hand, a positive Phalen and/or positive Tinel test, or positive electromyography. Therapy includes rest, temporary immobilization, NSAIDs, and surgery.
- **Cervical spine instability** may be observed in patients with established RA who have degeneration of the ligaments and bone in the C-spine area. Degeneration of the transverse ligament can lead to instability at the C1-C2 level. Minor trauma can lead to neurologic sequelae due to inherent instability.
- **Keratoconjunctivitis sicca** occurs in approximately 25% of patients with RA. Symptoms include ocular discharge, foreign body sensation, and dry eye. Episcleritis may progress to scleromalacia if untreated. Treatment includes referral to ophthalmology, artificial tears, systemic NSAIDs, topical NSAIDs, systemic steroids, and cyclophosphamide.

- Patients with an established diagnosis of RA who are being treated with DMARDS, particularly those treated with combination therapy including the biologic response modifying agents such as anti-TNF antibody therapy, may present with serious infections and/or malignancies.
- Additionally, adverse events from RA medications may include liver toxicity, renal toxicity, bone marrow depression, lung inflammation, and skin manifestations.
- Cardiovascular morbidity and mortality are enhanced in rheumatoid arthritis, which might be due to an increased prevalence of cardiovascular risk factors such as dyslipidemia.

DYSLIPIDEMIA[44,45,46,47,48]

Dyslipidemia is a disorder of lipoprotein metabolism, including lipoprotein overproduction or deficiency. Dyslipidemias may be manifested by elevation of the total cholesterol, the "bad" low-density lipoprotein (LDL) cholesterol and the triglyceride concentrations, and a decrease in the "good" high-density lipoprotein (HDL) cholesterol concentration in the blood. Serum cholesterol is distributed mainly among three major lipoprotein classes:

Very low density lipoproteins (VLDL) , Low density lipoproteins (LDL), & High density lipoproteins (HDL), with small amounts in intermediate density lipoproteins (IDL) and lipoproteins (a) . About 60–70% of cholesterol is contained in LDL.

Chylomicrons, the least dense type of cholesterol transport molecules, contain apolipoprotein B-48, apolipoprotein C, and apolipoprotein E in their shells. Chylomicrons are the transporters that carry fats from the intestine to muscle and other tissues that need fatty acids for energy or fat production. Cholesterol which is not used by muscles remains in more cholesterol-rich chylomicron remnants, which are taken up from the bloodstream by the liver.[49,50]

VLDL molecules are produced by the liver and contain excess triacylglycerol and cholesterol that is not required by the liver for synthesis of bile acids. These molecules contain apolipoprotein B100 and apolipoprotein E in their shell. During transport in the bloodstream, the blood vessel cleave and absorb more triacylglycerol from IDL molecules, which contain an even higher percentage of cholesterol. The IDL molecules have two possible fates: Half are into metabolism by HTGL, taken up by the LDL receptor on the liver cell surfaces and the other half continue to lose

triacylglycerols in the bloodstream until form LDL molecules, which have the highest percentage of cholesterol within them.

LDL molecules, therefore, are the major carriers of cholesterol in the blood, and each one contains approximately 1,500 molecules of cholesterol ester. The shell of the LDL molecule contains just one molecule of apolipoprotein B100, which is recognized by the LDL receptor in peripheral tissues. Upon binding of apolipoprotein B100, many LDL receptors become localized in clathrin-coated pits. Both the LDL and its receptor are internalized by endocytosis to form a vesicle within the cell. The vesicle then fuses with a lysosome, which has an enzyme called lysosomal acid lipase that hydrolyzes the cholesterol esters. Now within the cell, the cholesterol can be used for membrane biosynthesis or esterified and stored within the cell, so as to not interfere with cell membranes.[51,52,]

HDL particles are thought to transport cholesterol back to the liver for excretion or to other tissues that use cholesterol to synthesize hormones in a process known as reverse cholesterol transport (RCT). Having large numbers of large HDL particles correlates with better health outcomes. In contrast, having small numbers of large HDL particles is independently associated with atheromatous disease progression within the arteries.[53,54]

Purpose of lipid tests [55,56,57,58]

The purpose of blood lipid testing is to determine whether abnormally high or low concentrations of a specific lipid are present. Low levels of cholesterol are associated with liver failure and inherited disorders of cholesterol production. Cholesterol is a primary component of the plaques that form in atherosclerosis and is therefore the major risk factor for the rapid progression of coronary artery disease (CAD). High blood cholesterol may be inherited or result from such other conditions as biliary obstruction, diabetes mellitus, hypothyroidism, and nephrotic syndrome. In addition, cholesterol levels may be increased in persons who eat foods that are rich in saturated fats and cholesterol, and who lead a sedentary lifestyle.

To measure LDL-cholesterol directly, the LDL fraction in the serum has to be isolated by ultracentrifugation, followed by measurement of the cholesterol content. The process requires complicated technique and costly instrumentation. In contrast, the Friedewald method doesnot require additional measurement other than total cholesterol, HDL-cholesterol, and triacylglycerol. Prolongation of fasting time beyond 12 h is not necessary for determination of blood lipid levels.[59,60]

LDL cholesterol is estimated by use of the Friedewald formula:

LDL-C = [Total-C - HDL-C - (0.2 x TGL)]

Low levels of triglyceride are seen in persons with malnutrition or malabsorption. Increased levels are associated with diabetes mellitus, hypothyroidism, pancreatitis, glycogen storage diseases, and estrogens. Diets rich in either carbohydrates or fats may cause elevated triglyceride levels in some persons. Although triglycerides are not a component of the plaque associated with atherosclerosis, they increase the viscosity (thickness) of the blood and promote obesity, which can contribute to coronary disease. The majority of cholesterol and triglyceride testing is performed to screen persons at increased risk of coronary artery disease.[61,62]

Precautions before performing lipid tests[63,64]

Tests for triglycerides and LDL cholesterol must be performed following a 12-hour fast. Acute illness, high fever, starvation, or recent surgery lowers the blood cholesterol and triglyceride levels. If possible, patients should also stop taking any medications that may affect the accuracy of the test.

Patients who are scheduled for a lipid profile test should fast (except for water) for 12 to 14 hours before the blood sample is drawn. If the patient's LDL cholesterol is to be measured, he or she should also avoid alcohol for 24 hours before the test. When possible, patients should also stop taking any medications that may affect the accuracy of the

test results. These drugs include corticosteroids ; estrogen or androgens; oral contraceptives; some diuretics ; antipsychotic medications, including haloperidol; some antibiotics ; and niacin. Antilipemics are drugs that lower the concentration of fatty substances in the blood. When these medications are taken by the patient, blood testing may be done frequently to evaluate liver function as well as lipid levels.

ATP III Guidelines[32]

To determine lipoprotein levels– obtain complete lipoprotein profile after 9- to 12-hour fast.

ATP III Classification of LDL, Total, and HDL Cholesterol (mg/dL)

Primary Target of Therapy[32,33]

LDL Cholesterol

<100	Optimal
100-129	Near optimal/above optimal
130-159	Borderline high
160-189	High
>190	Very high

Total Cholesterol

<200	Desirable
200-239	Borderline high
>240	High

HDL Cholesterol

<40	Low
>60	High

Serum Triglycerides (mg/dL)

<150	Normal
150-199	Borderline high
200-499	High
>500	Very high

Comparison of LDL Cholesterol and Non-HDL Cholesterol Goals for Three Risk Categories

Risk Category	LDL Goal (mg/dL)	Non-HDL Goal (mg/dL)
CHD and CHD Risk Equivalent (10-year risk for CHD >20%)	<100	<130
Multiple (2+) Risk Factors and 10-year risk <20%	<130	<160
0-1 Risk Factor	<160	<190

(CHD risk equivalent)

- Clinical CHD
- Diabetes is regarded as a CHD risk equivalent.
- Symptomatic carotid artery disease

- Peripheral arterial disease
- Abdominal aortic aneurysm

Major Risk Factors (Exclusive of LDL Cholesterol) That Modify LDL Goals[65,66]

- Cigarette smoking
- Hypertension (BP >140/90 mmHg or on antihypertensive medication)
- Low HDL cholesterol (<40 mg/dL)*
- Family history of premature CHD (CHD in male first degree relative <55 years; CHD in female first degree relative <65 years)
- Age (men >45 years; women >55 years)
- HDL cholesterol >60 mg/dL counts as a "negative" risk factor; its presence removes one.

Importantly, the reduction in HDL-C has as a consequence the increase in the TC/HDL-C ratio. This ratio represents an **atherogenic index**, which is an important prognostic marker for cardiovascular disease.[15] Indeed, the risk of myocardial infarction increases considerably when this ratio is higher than five, and it should ideally be four or less.[33] The serum TC and HDL-C levels in RA are inversely correlated with disease activity suggesting a potential role for inflammation in the atherogenic profile and the higher atherosclerotic risk observed in RA.[33]

Total Cholesterol/HDl Cholesterol[67,68]

This ratio becomes high when the total cholesterol increases and HDL cholesterol decreases. Low ratio indicates lower risk of heart attack, while high ratio indicates higher risk. The total/HDL becomes low for low total cholesterol and high HDL cholesterol values. The safe total/HDL ratio is less than 4. Total/HDL is more commonly obtained because the total cholesterol is easier and cheaper to obtain. A value more than 5 indicates high risk for coronary artery disease.

LDL/HDL Ratio
[LDL Cholesterol / HDL Cholesterol]

The LDL/HDL ratio is more important ratio than total cholesterol/HDL because LDL is a measure of bad cholesterol and HDL is a measure of good cholesterol. LDL/HDL is therefore an accurate measure of heart disease although it is costly to measure LDL cholesterol.

The risk levels of different values of LDL/HDL ratios are:

Risk Level	**LDL/HDL Ratio**
Low risk	3.3 - 4.4
Average risk	4.4 - 7.1
Moderate risk	7.1 - 11.0
High risk	>11.0

The role of LDL-C in the pathogenesis of CHD has been established. Nevertheless, there are some patients with CHD with plasma LDL-C levels within the normal range. The variation in size, density, and composition of the LDL-C particle governs its properties. The use of gradient gel electrophoresis has demonstrated the existence of two distinct LDL-C phenotypes. The larger, less dense particles are known as pattern A and the smaller, denser particles are known as pattern B. These small, dense LDL-C particles are more prevalent in patients with the atherogenic metabolic syndrome (low HDL-C and high TG levels) and those with CHD.[35,36,37,38]

Within the realms of the standard lipid profile, non-HDL appears to be the parameter correlating best with apo B. It therefore appears prudent to establish non-HDL-C as a target for modification of CVD death risk.

In both males and females, non-HDL-C predicted CVD death better than LDL-C, with increasing levels of non-HDL-C corresponding to an increased risk of CVD mortality. In addition, for female patients, only HDL-C and non-HDL-C significantly predicted CVD death, while the currently targeted lipoprotein, LDL-C, did not correlate with outcomes. In fact, LDL-C levels were the least reliable predictor of CVD deaths in women, when compared with non-HDL-C and HDL-C.[38]

HDLs are particles with numerous atheroprotective functions, including facilitation of reverse cholesterol transport, improvement of endothelial function, protection of LDL from oxidation , limitation of hemostasis and retardation of inflammatory activity related to the vascular wall.

During the last decade interest has focused on apolipoprotein A-1 (apo A-1), apolipoprotein B (apo B) and lipoprotein(a) (Lp(a). Apo A-1 is the protein present on the HDL-C particles, whereas apo B is found on the LDL-C, very low density lipoprotein (VLDL) and chylomicrons particles. Hence, assessment of plasma apo A-1 and apo B allow an assessment of the total number of anti-atherogenic and atherogenic particles, respectively. Lp(a) is modified form of LDL in which apo A-1 is bound to apo B.

There is some evidence that apo B might be a better predictor for cardiovascular events than LDL-C and that the apo B/apo A-1 ratio is an accurate risk factor for cardiovascular disease (Rader et al 1994; Walldius and Jungner 2006)[91]. In other words: Apo A-1 might protect against cardiovascular disease whereas apo B might increase the cardiovascular risk.

ATHEROSCLEROSIS[69,70,71]

Atherosclerosis is a multifactorial and dynamic process. One of its feature is the presence of fatty streaks along the vessel wall leading to build-up of plaques on the wall of arteries, which leads to reduction in caliber of vessels. [22,23] Vasomotor function, the thrombogenicity of the blood vessel wall, the state of activation of the coagulation cascade, the fibrinolytic system, smooth muscle cell migration and proliferation, and cellular inflammation are complex and interrelated biological processes that contribute to atherogenesis and the clinical manifestations of atherosclerosis.[22,23]

The lesions of atherosclerosis do not occur in a random fashion. Hemodynamic factors interact with the activated vascular endothelium. Fluid shear stresses generated by blood flow influence the phenotype of the endothelial cells by modulation of gene expression and regulation of the activity of flow-sensitive proteins.

Atherosclerotic plaques characteristically occur in regions of branching and marked curvature at areas of geometric irregularity and where blood undergoes sudden changes in velocity and direction of flow. Decreased shear stress and turbulence may promote atherogenesis at these important sites within the coronary arteries, the major branches of the

thoracic and abdominal aorta, and the large conduit vessels of the lower extremities.

The physical signs of atherosclerosis provide objective evidence of extracellular lipid deposition, stenosis or dilatation of large muscular arteries, or target organ ischemia or infarction.

Hyperlipidemia - Xanthelasma, tendon xanthomata

Coronary artery disease - Fourth heart sound, tachycardia, hypotension, hypertension

Cerebrovascular disease - Diminished carotid pulses, carotid artery bruits, focal neurological deficits

Peripheral vascular disease - Decreased peripheral pulses, peripheral arterial bruits, pallor, peripheral cyanosis, gangrene, ulceration

Abdominal aortic aneurysm - Pulsatile abdominal mass, peripheral embolism, circulatory collapse.

Atheroembolism - Livedo reticularis, gangrene, cyanosis, ulceration (The presence of pedal pulses in the setting of peripheral ischemia suggests microvascular disease and includes cholesterol embolization.)

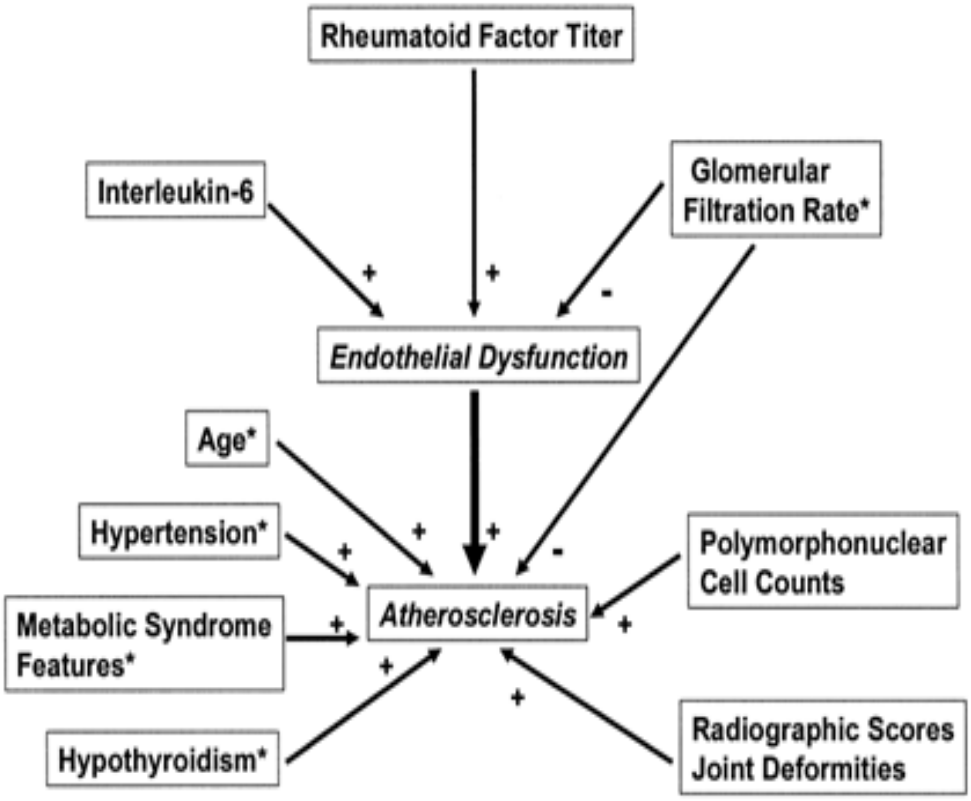
Valvular heart disease (particularly calcific aortic stenosis, now recognized to be linked to atherosclerosis) – Cardiac murmur

Dyslipidemia & accelerated atherosclerosis in rheumatoid arthritis

Cardiovascular manifestations are frequent in rheumatoid arthritis (RA) and significantly contribute to morbidity and mortality in this disorder. Premature atherosclerosis is responsible for these complications, as supported by autopsy studies. Moreover, a high prevalence of sub-clinical atherosclerosis, as evaluated by imaging and instrumental parameters, has been reported. Traditional risk factors cannot completely account for accelerated atherosclerosis in RA.[72,73,74]

Factors for CV events in RA includes mainly classical risk factors for CAD as in general population, **dyslipidemia** , long term use of **steroids** , older age of diagnosis and long disease duration and persistent disease activity.[17]

Immunological and metabolic laboratory markers, anticyclic citrullinated peptide (anti-CCP) antibodies, IgM rheumatoid factor, circulating immune complexes, pro-inflammatory cytokines including tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), Th0/Th1 T cells, high homocysteine, dyslipidemia, decreased folate and vitamin B12 production, and impaired paraoxonase activity may all be involved in the development of vascular disease in RA.



In general, and with some variations between different studies, the lipid profile of patients with active or untreated RA is primarily characterized by a decrease in serum levels of HDL-C whereas contrasting results have been published on the serum levels of TC, TGL and LDL-C. Importantly, the reduction in HDL-C has as a consequence the increase in the TC/HDL-C ratio. This ratio represents an atherogenic index, which is an important prognostic marker for cardiovascular disease. Indeed, the risk of myocardial infarction increases considerably when this ratio is higher than five, and it should ideally be four or less. The serum TC and HDL-C levels in RA are inversely correlated with disease activity, suggesting

a potential role for inflammation in the atherogenic profile and the higher atherosclerotic risk observed in RA.[15]

The cholesterol ester transfer protein (CETP) has a central role in HDL metabolism and in the regulation of HDL-C levels in serum. CETP exchanges cholesterol esters with triglycerides between HDL and apolipoprotein B-containing lipoproteins and thus significantly contributes to the reverse cholesterol transport pathway. High levels of CETP activity lead to a reduction in HDL-C levels and an atherogenic lipoprotein profile.[15] The role of this plasma protein in HDL metabolism is highlighted by the discovery that genetic CETP deficiency is the main cause of high HDL-c levels in Asian population.[75] Torcetrapib, a CETP inhibitor, was a drug being developed to treat hypercholesterolemia. Its development was halted in 2006 when phase III studies showed excessive all cause mortality in the treatment group receiving a combination of atorvastatin and the study drug.[18]

Nevertheless, rheumatoid arthritis patients appear to have a high prevalence of abnormal blood lipid profiles—and given that so few of our patients were receiving lipid-lowering therapy, it is clear that we are not managing traditional risk factors for cardiovascular disease as part of our routine care.[39]

Data from the trial of atorvastatin in rheumatoid arthritis demonstrated that patients who received atorvaststin 40 mg had improvement in disease severity scores, swollen joint counts, and inflammatory markers with no increase in adverse events compared to placebo.[39] Whilst the routine use of statins as disease-modifying therapy for patients with rheumatoid arthritis is not yet routine, practising their use in selected patients with abnormal lipid profiles could also benefit their arthritis.

Patients with RA have a higher prevalence of the metabolic syndrome than control subjects. Inflammation-associated metabolic syndrome is a mechanism that may contribute to increased coronary-artery atherosclerosis in RA.

In many studies, early RA patients exhibited higher serum levels of (TC), (LDL-C) and TGL compared to controls. (HDL-C) levels were significantly lower compared to controls.[15] Importantly, the serum HDL- C and apoA-I levels were significantly lower compared to controls. As a consequence, the atherogenic ratio of TC/HDL-C as well as that of LDL-C/ HDL-C was significantly higher in ERA patients compared to controls.

Analysis of blood samples from blood donors who later went on to develop rheumatoid arthritis (in a recent dutch study)

showed that, their total cholesterol was higher, HDL was lower and TGL were higher than levels of controls.[11] As inflammation only marginally explains the differences between the two groups, a modulating effect of lipids on inflammatory processes is hypothesised.

The dyslipidemia observed in RA appears to be dependent on disease activity, ie, a higher disease activity is associated with lower total cholesterol levels and even more depressed high density lipoprotein levels, leading to a higher (ie, unfavorable) atherogenic index. It appears that this dyslipidemia is already present long before the clinical onset of rheumatoid arthritis.[9]

This decrease in TC and LDL levels might result from their increased catabolism or increased retention (ie, subendothelial deposition) rather than decreased lipid production. Subendothelial lipid deposition might explain the paradox of lower cholesterol levels and increased CV risk in RA. Indeed, low cholesterol concentrations have been previously associated with high mortality risk and a poor response to tissue stress.[76,77] Reduced levels of the lipid soluble antioxidant alpha-tocopherol (in RA patients) which terminates the process of lipid peroxidation, points to increased oxidative activity. In RA patients, low levels of HDL-cholesterol have been found, which return to normal with treatment. However there are

conflicting results for levels of other lipoprotein in RA, which may be explained by steroid treatment, renal disease and altered catabolic states.[10]

Systemic inflammation may also play a role in the development of atherosclerosis . In fact, the increase of acute phase reactants in cardiovascular events has already been documented. It has even been suggested that RA and atherosclerosis may share a common predisposition factor ; CRP is the common denominator for both diseases . CRP, which increases in active disease, may contribute to atherosclerosis because it stimulates macrophages to produce tissue factor, a procoagulant that is found in atherosclerotic plaques. The presence of CRP in atheromatic lesions also suggests a 'cause and effect' relationship between this acute phase reactant and coronary events.[15]

Corticosteroids, on the other hand, have a potentially atherogenic effect, given that they cause dyslipidemia and hypertension . In spite of this, the effect of their long-term administration in RA is not yet completely understood.

Several studies have been unable to demonstrate any association between cardiovascular mortality and the use of corticosteroids . A recent study reported a small or no increase in TC levels during long-term administration of corticosteroids [16.] Corticosteroids can contribute

to a type 2b hyperlipidaemia. The triglyceride level , LDL and HDL values may often rises with prednisolone treatment.[10]

ERA patients are characterized by an atherogenic lipid profile, which improves after therapy. Thus, early immuno-intervention to control disease activity may reduce the risk of the atherosclerotic process and cardiovascular events in ERA patients.[15]

Carotid artery intima media thickness (CIMT)

Carotid intima-media thickness (cIMT) reflects early atherosclerosis and predicts cardiovascular events in the general population. An increased cIMT is present in patients with rheumatoid arthritis, compared with control individuals, from the early stages of the disease and is thought to indicate accelerated atherosclerosis, but direct evidence is not available. Whether cIMT is susceptible to rapid and potentially reversible change depending on the intensity of inflammation in states of high-grade systemic inflammation, such as rheumatoid arthritis, remains unknown.[8]

Ultrasonographic evaluation of carotid artery intima media thickness (CIMT) allows the non-invasive and early detection of atherosclerotic changes and is used as a non-invasive end point for assessing the progression and regression of atherosclerosis in clinical trials. Because atherosclerosis is a systemic disease, assessment of carotid plaque by

ultrasonography provides a robust, direct measure of systemic atherosclerosis.[78]

Carotid IMT is related to coronary risk factors such as age, smoking, hypertension and LDL-Cholesterol. Several studies suggest that CIMT is of high value as a surrogate marker for generalized atherosclerosis and atherosclerosis of coronary arteries. Hence non-invasive ultrasonographic measurement of IMT can be of great value in screening for such asymptomatic patients suffering from RA.[12]

The CIMT has been shown in numerous studies to be a non-invasive, economical, reliable and sensitive marker for atherosclerosis. To measure the CIMT, duplex scanning of the carotid arteries is performed. This refers to the use of Doppler (to estimate blood flow characteristics) in conjunction with conventional 2-dimensional (B-mode) ultrasound. Depending on the scanning protocol used, specific pre-determined bilateral sites in the vicinity of the carotid bifurcation are selected for measurement of parameters. The images obtained using the B-mode scan are then measured for the intima-media thickness, while the Doppler assessment is used to gauge the impedence to blood flow caused by the narrowing induced by the plaque. Use of computer software can provide a more accurate reading, a reduction in analysis time and elimination of inter-observer bias.[41,42]

Since arterial wall area incorporates both diameter and wall thickness, area estimation may provide some advantages to IMT alone . The relationship of plaques, IMT, and artery diameter is complex and a number of arterial phenotype classifications have been proposed. Risk factors are associated with arterial wall thickness, IMT progression, artery diameter , and calcified carotid plaques.

Correlations between carotid IMT and diameter (0.31 to 0.62) vary across populations and may depend upon whether the internal or external diameter [31] is evaluated. Part of the correlation may reflect an adaptive process used to maintain arterial wall stress, but in the presence of vulnerable atherosclerotic plaques, arterial diameter may reflect direct damage of the internal elastic lamina and arterial media [36,37]. So, risk factors may contribute to IMT and diameter directly and indirectly.

Given the strong body of evidence for its use, carotid doppler and CIMT should become routine screening tools for atherosclerosis in India. We have a population with a high incidence of diabetes, a high prevalence of dyslipidemia and, with increasing urbanization, an everincreasing population with detrimental lifestyle changes.

It provides a noninvasive, readily available method to image the major arteries of the neck. Its validity as a measure of atherosclerosis is supported by **3 lines of evidence**:

(1) the correlation between ultrasound and histological measurements of arterial intima-media thickness (IMT);(2) the correlation between histological measurements of carotid and coronary wall IMT; and (3) the association between CV risk factors and ultrasound measurements of carotid IMT, and the ability of the latter to predict CV events in the general population.[84,85]

A relatively new measure, the coronary artery inter-adventitial distance, is also being evaluated and has been found to be a good predictor of cardiovascular risk. Recently, the ankle-brachial index has also been studied as a clinical aid to estimate subclinical atherosclerosis and its use has been suggested as a precursor to CIMT measurement.[43]

DYSLIPIDEMIA & ATHEROSCLEROSIS – MEDICATION[25]

The most common type of medicine to treat hypercholesterolemia are **'statin'** drugs. They work by inhibiting the enzyme HMG-CoA Reductase. Statin drugs lower the amount of LDL cholesterol in the blood which stops atherosclerosis from getting worse. Statin drugs can even help make atherosclerosis better. However, statins are not as good at increasing the HDL cholesterol. Low HDL is hard to treat with medicines, but goes up with more exercise! Statins can cause liver problems and damage to muscle cells.

Fibrates are used in (STATIN+) combination therapy & also as monotherapy agents. Fibrates reduce the number of non-fatal heart attacks, but do not improve all-cause mortality and are therefore only indicated in those not tolerant to statins. Although less effective in lowering LDL, fibrates improve HDL and triglyceride level and seem to improve insulin resistance when the dyslipidemia is associated with other features of the metabolic syndrome. Fibrates are agonists of the PPAR-α receptor in muscle, liver, and other tissues. Most fibrates can cause mild stomach upset and myopathy. Since fibrates increase the cholesterol content of bile, they increase the risk for gallstones.

Bile Acid Resins (cholestyramine) are medicines that make people not absorb as much bile when they digest food. This causes them to take up less cholesterol also, which lowers blood levels of cholesterol. **Niacin** is used to treat hypercholesterolemia. Niacin is one of the medicines that may make HDL (good) cholesterol go up. The biggest problem with taking enough Niacin to help cholesterol is that it causes severe flushing (hot, red, sometimes itchy skin). **Ezetimibe** is a drug that acts by decreasing cholesterol absorption in the intestine. It may be used alone when other cholesterol-lowering medications are not tolerated, or together with statins when statins alone do not control cholesterol.

AIMS AND OBJECTIVES

1) To study the Serum Fasting Lipid Profile Pattern in Rheumatoid arthritis.
2) To estimate subclinical atherosclerosis in patients suffering from rheumatoid arthritis by measuring the carotid intima media thickness.
3) To study the association of age, duration of illness, CRP, disease activity& RA factor with dyslipidemia & carotid intima media thickness in these patients.
4) To analyse lipid parameters and CIMT and its correlation with DAS 28 score. (Disease activity score)

MATERIALS AND METHODS

Setting	:	Department of Medicine. Govt. Rajaji Hospital
Design	:	Cross–sectional case control study.
Period of study	:	Six months (July 2010 to December 2010)
Ethical approval	:	Obtained from ethical committee headed by Dean, Govt. Rajaji Hospital.
Consent	:	Obtained from all patients.
Statistical software	:	EPI Info 2008.
Study population	:	Patients attending Rheumatology OP with Rheumatoid Arthritis- randomly selected.

Inclusion criteria:

1) Patients who satisfied Revised American Rheumatologic Association criteria 1987, irrespective of sex and duration of disease and with age more than 18 years.
2) Forty healthy control subjects who were willing to participate after informed consent.

Exclusion criteria:

1) Patients already on lipid lowering medications.
2) Previous history of coronary artery disease or cerebrovascular disease.

3) Those who had deranged liver function tests and those who are suffering from inherited disorders of lipid and lipoprotein metabolism and/or family history of such disorders.
4) Serum creatinine level of 1.6 mg/dl or greater.
5) Current or recent (within the past 3 months) pregnancy or use of OCPs.
6) Patients who were smokers and/or alcoholics or with features of peripheral occlusive vascular disease who already took treatment.
7) Patients who are known diabetics and/or hypertensives or detected now at the time of study.
8) Patients on eltroxin or with clinical evidence of hypothyroidism.
9) Those who have mixed disorder like SLE and RA; SS and RA; and MCTD and overlap syndrome.
10) Obesity (body mass index >30).

Forty two patients attending Rheumatology clinic, Govt. Rajaji Hospital, Madurai, who were diagnosed to have Rheumatoid Arthritis, and who satisfied the inclusion and exclusion criteria were selected for the study.

Forty controls attending general medical op for minor ailments and who were otherwise healthy were also included.

The selected patients were evaluated with history regarding the duration of disease, nature of symptoms, history of drug intake, and the type of onset of symptoms

Presence of joint swelling, tenderness, and deformities and number of tender joints, number of swollen joints were noted. Detailed clinical examination including pallor and rheumatoid nodules were done. All systems were examined carefully. Visual analogue pain score was carefully assessed. A detailed cardiovascular examination was done with special attention to blood pressure recording, carotid bruit and checking peripheral pulses and other markers of atherosclerosis.

Serum Fasting Lipid Profile, Hemoglobin, White blood cell count, Differential count, Blood Urea, Serum Creatinine, Blood sugar, ESR, LFT, Rheumatoid Factor and C Reactive Protein by latex agglutination test , ECG , TSH, Chest X ray and Carotid Doppler study of CCA & ICA to detect the mean CIMT were done for all patients.

Disease Activity Score, BMI, Total Cholesterol / HDL & LDL / HDL ratios were calculated for every patients. Carotid Doppler study, Total Cholesterol / HDL & LDL / HDL ratios were calculated for all control subjects also.

DAS 28 score

Disease activity score is a composite score using tender and swollen joint count, ESR and patient's global assessment activity using a 10 mm visual analogue scale.

DAS28= 0.56 √(tender joints) + 0.28√(swollen joints)
+ 0.70 Log (ESR) + 0.014(VAS in mm)

Classification

Less Active	≤ 3.1
Moderate	3.2- 5.1
Highly active	> 5.1

(Minimum score= 0; Maximum score= 9)

ASSESSMENT OF CAROTID INTIMA MEDIA THICKNESS[46]

Ultrasonographic scanning of the carotid arteries was performed using WIPRO – Ge logic 400 MD scanner with a linear transducer (midfrequency range 7.5 – 10 MHz). The patient being in supine position and the chest being elevated with a pillow and the head being turned to the opposite side of the carotids examined, the probe was placed on the medial side of the sternocleidomastoid muscle to identify the carotid vessel and the carotid bulb was traced. Intima media thickness was assessed at the site of maximum thickness in the CCA / Bulb / ICA.

The carotid wall shows parallel echogenic lines separated by a hypoechoic region (media). The inner line is the lumen intima interface

and the outer is the media adventitia interface. Carotid IMT was defined as the distance from the leading edge of the first echogenic line to the leading edge of the second echogenic line on the scans. Carotid IMT was measured on both sides and the average value was taken as the mean CIMT. IMT value of more than 0.7-0.8mm is suggestive of significant atherosclerosis.[45]

Confict of interest : There was no conflict of interest.

Financial support : Nil

Statistical analysis :

The information collected regarding all the selected cases were recorded in a Master chart in Microsoft Excel spread sheet. Data analysis was done with the help of computer using Epidemiological Information Package **(EPI 2008)**. Using this software, range, frequencies, percentage, mean, standard deviation and p value were calculated. Kruskul Wallis chi-square test was used to test the significance of difference between quantitative variables and Yate's test for qualitative variables. A 'p' value less than 0.05 was taken as significant.

RESULTS AND ANALYSIS

Profile of total cases studied:

- Majority of patients were from in and around Madurai city.
- The total number of patients included in the study was 42.

  [FEMALE (F)-33 ; MALE (M)-9].
- Fourty age and sex [F-30/M-10] matched controls from in and around Madurai were also included in the study for comparative analysis.
- Mean age of study group was 40.2 years and that of control group was 41.7 years.
- Only 3 patients had **no** previous history of any treatment.
- Lipid profiles and CIMT of all patients were compared with the control group matched for sex, age, and body mass index.

TABLE – 1A

AGE GROUP DISTRIBUTION IN STUDY AND CONTROL GROUP

	STUDY GROUP	CONTROL GROUP
TOTAL NO OF CASES	42	40
Age group		
UP TO 20 YEARS	1	0
21- 30 YEARS	4	5
31-40 YEARS	17	12
41-50 YEARS	12	14
ABOVE 50 YEARS	8	9
MEAN AGE	40.2	41.7
P VALUE - 0.654 (NOT SIGNIFICANT)		

Mean age of study group was 40.2 years and that of control group was 41.7 years.
There was no significant difference in age between study and control group

TABLE **1B** **SEX DISTRIBUTION IN BOTH GROUPS**

SEX	STUDY CASES		CONTROL CASES	
	NUMBER	PERCENTAGE	NUMBER	PERCENTAGE
MALE	9	21.4%	10	25%
FEMALE	33	78.6%	30	75%

P VALUE - 0.677 (NOT SIGNIFICANT). There was no significant difference.

TABLE 1C -

DURATION OF ILLNESS IN STUDY GROUP

DURATION (in years)	NUMBER OF CASES	PERCENTAGE
0-5	23	54.8 %
6-10	16	38.1 %
>10	3	7.1 %
TOTAL	42	
MEAN DURATION	5.1 YEARS	

The mean duration of illness in the study was **5.1 years**.

TABLE 1D **HISTORY OF PREVIOUS TREATMENT**

HISTORY OF TREATMENT	STUDY CASES NO.	PERCENTAGE
YES	39	92.9 %
NO	3	7.1 %
TOTAL	42	

Only 3 patients had **no** previous history of any treatment.

TABLE 1E **CRP IN STUDY GROUP AND CONTROL GROUP**

CRP	**STUDY GROUP**	**CONTROL GROUP**
POSITIVE	37	8
NEGATIVE	5	32
P VALUE	**0.0001(SIGNIFICANT) CRP significantly high in study group.**	

TABLE 1F

ESR IN STUDY GROUP AND CONTROL GROUP

ESR	Study group	Control group
Range	29-109	4-46
Mean	60	16
SD	18	10
P VALUE - 0.0001 (SIGNIFICANT)		

The mean ESR value in RA patients was about **4 times higher** when compared to the control population.

TABLE 1G

DAS SCORE AMONG STUDY GROUP

DAS SCORE		NUMBER	[PERCENTAGE]
<3.1	LESS ACTIVE	6	14.3%
3.2 – 5.1	ACTIVE	20	47.6%
>5.1	HIGHLY ACTIVE	16	38.1%

The mean DAS SCORE was **4.68.**

Sixteen patients had a **highly active** disease.

TABLE NO 2A

Table for biochemical and lipid profile in study and control subjects

PARAMETER	STUDY GROUP			CONTROL GROUP		P VALUE	SIGNIFICANCE
	MEAN	SD		MEAN	SD		
TOTAL CHOLESTEROL	177.9	27.2		170.2	22.3	0.284	NOT SIGNIFICANT
TRIGLYCERIDE	151.1	33.4		117.4	22.6	0.0001	**SIGNIFICANT**
VLDL	30.9	7.4		23.5	4.5	0.0007	**SIGNIFICANT**
HDL	37.6	7.4		46.4	7.3	0.0001	**SIGNIFICANT**
LDL	108.9	25.4		100.4	18.9	0.105	NOT SIGNIFICANT
NON-HDL CHO	141.2	28.2		123.8	20.6	0.019	**SIGNIFICANT**
BMI	21.1	2.2		22.9	2.0	0.641	NOT SIGNIFICANT
SYS.BP/DI BP	115/74	12/4		114/72	11/5	SBP 0.81 DBP0.70	NOT SIGNIFICANT
Hemoglobin	11.0	1.4		11.6	1.5	0.069	NOT SIGNIFICANT
Urea	30.1	6.1		29.5	6.7	0.673	NOT SIGNIFICANT
Creatinine	0.75	0.13		0.73	0.16	0.608	NOT SIGNIFICANT

The Triglyceride level , VLDL level & non – HDL cholesterol values were **significantly higher** in RA patients.

HDL cholesterol values were **significantly lower** in RA patients.

There was **no significant difference** in Total Cholesterol and LDL values between RA patients and the control population.

TABLE 2 B - CAROTID INTIMA MEDIA THICKNESS AND ATHEROGENIC INDEX IN STUDY & CONTROL GROUP

GROUP	CIMT (MM)	LDL/HDL	TOTAL CHOL/HDL
	(MEAN±SD)	(MEAN±SD)	(MEAN±SD)
RA PATIENTS	0.68 ± 0.08	3.24 ±0.95	5.44 ± 1.15
CONTROL GROUP	0.58 ± 0.07	2.08± 0.67	3.59 ± 0.78
P VALUE	**0.032 SIGNIFICANT**	**0.0001 SIGNIFICANT**	**0.0001 SIGNIFICANT**

The **CIMT** was **significantly** higher in RA patients.

The **LDL / HDL** ratio was **significantly** higher in RA patients.

The **Total Cholesterol / HDL** ratio was also **significantly** higher in RA patients.

TABLE 3A- **AGE & CAROTID INTIMA MEDIA THICKNESS IN STUDY & CONTROLS**

AGE GROUP	CAROTID INTIMA MEDIA THICKNESS (cm)			
	STUDY GROUP		CONTROL GROUP	
	MEAN	SD	MEAN	SD
LESS THAN 20 YRS	0.6	0	---	---
21 – 30 YRS	0.6	0.07	0.56	0.06
31 - 40 YRS	0.63	0.05	0.57	0.05
41 - 50 YRS	0.67	0.05	0.58	0.04
MORE THAN 50 YRS	0.71	0.07	0.62	0.06

CIMT was **higher** in all age groups in RA patients when compared to control population

TABLE 3B - **LIPID PROFILE & CIMT IN RA patients & CONTROLS**

PARAMETER	RA PATIENTS			CONTROL GROUP	
	NUMBER(42)	PERCENT		NUMBER(40)	PERCENT
TGL> 150	19	45.2%		05	12.5%
LDL > 100	22	52.3%		19	47.5%
HDL<40	26	61.9%		09	22.5%
NON – HDL >160	06	14.3%		01	02.5%
LDL/HDL>3	24	57.1%		02	05.0%
TOT. CHO/HDL>4	32	76.2%		07	17.5%
TOT. CHO/HDL>5	21	50.0%		02	05.0%
CIMT>7.2 mm	13	30.9%		04	10.0%

LDL, HDL, TRIGLYCERIDE LEVELS cut off limits taken according to NCEP–III guidelines previously mentioned.

Values of mean CCA IMT above mean + 2 SD of the control group were defined as abnormal IMT. This Criteria is taken as in the study mentioned from (J Rheumatol 2006;33:244-7). August 28, 2005. Sundeep grover etal - A study on Subclinical Atherosclerosis in Rheumatoid Arthritis in India , August 28, 2005. Prof. R. Misra, Department of Immunology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow.

- The *CIMT* more than upper limit was seen in **13** RA patients(30.9%) . Among the RA group, **24** patients (**57%**) had *LDL / HDL ratio >3* **Ten** RA patients had LDL/HDL ratio > 4.
- Interestingly**, 21** RA patients (50%) had *Total Chol/ HDL ratio> 5* while only 5% of control population had such an **atherogenic profile**.
- *HDL cholesterol* values were lower(<40) in **26** (62%) of RA patients as compared to only 22% of controls.
- The *triglyceride* values were **higher** (45.2%) in RA group .There was no significant difference in LDL values.
- Of the **13 RA patients** with *CIMT > 7.2mm* , SIX patients had *LDL/HDL > 4* and SEVEN patients had *TOTAL CHO/HDL > 5, and* ELEVEN **(85%)** patients had *HDL level <40 mg/dl.*

Table 3C-

ATHEROGENIC INDEX & CIMT IN RELATION TO DAS SCORE

DAS SCORE		LDL/HDL	TOTAL CHOL/HDL	CIMT(mm)
< 3.2	MEAN	3.45	5.54	6.9
	SD	0.35	0.73	0.7
3.2 – 5.1	MEAN	2.60	4.8	6.6
	SD	0.42	0.6	0.8
>5.1	MEAN	3.53	4.9	7.1
	SD	0.49	0.56	0.7
P VALUE		0.3939 (NOT SIGNIFICANT)	0.463 (NOT SIGNIFICANT)	0.185 (NOT SIGNIFICANT)

There was **no relation** between DAS score and atherogenic index or CIMT values.

TABLE 3D - DISEASE DURATION AND DYSLIPIDAEMIA AND CIMT

DISEASE DURATION	LDL/HDL (MEAN)	TOTAL CHOLESTEROL/HDL (MEAN)	CIMT (mm) (MEAN)
FIVE OR LESS YEARS	3.06	5.05	6.6
MORE THAN FIVE YEARS	3.48	5.68	7.4
P VALUE	**0.036 (SIGNIFICANT)**	**0.015 (SIGNIFICANT)**	**0.027 (SIGNIFICANT)**

RA patients with more than 5 years disease duration had a higher atherogenic index and higher CIMT than those with less than 5 years of illness.

TABLE 4

COMPARISON BETWEEN CRP POSITIVE & NEGATIVE CASES

PARAMETER	CRP POSITIVE		CRP NEGATIVE		P VALUE
	MEAN	SD	MEAN	SD	
TRIGLYCERIDE	156.5	38.9	147.1	30.8	0.261 (NOT SIGNIFICANT)
LDL	112.3	26.6	105.8	21.2	0.171 (NOT SIGNIFICANT)
HDL	36.2	6.3	45.4	8.8	**0.001 (SIGNIFICANT)**
NON HDL	149.2	31.5	138.9	24.4	0.193(NOT SIGNIFICANT)
Total Cholesterol	184.3	27.3	171.9	23.1	0.078 (NOT SIGNIFICANT)
LDL/HDL	3.33	1.0	2.31	0.8	**0.0001(SIGNIFICANT)**
TOTAL CHOL/HDL	5.5	1.2	4.3	1.1	**0.0003(SIGNIFICANT)**
CIMT (mm)	7.1	0.56	6.8	0.46	0.195(NOT SIGNIFICANT)
DAS SCORE	4.38	0.45	4.24	0.58	0.30(NOT SIGNIFICANT)

Out of the total 42 study patients, **37** (88.1%) were **CRP positive**.

The **LDL / HDL** ratio was significantly **higher in CRP POSITIVE** patients.

The **Total Cholesterol / HDL** ratio was significantly **higher in CRP POSITIVE** patients.

HDL cholesterol values were significantly **lower in CRP positive** patients.

There was **no significant difference** in Total Cholesterol, Triglyceride, Non-HDL , LDL Cholesterol & CIMT values between CRP positive and negative patients.

TABLE 5A

Rheumatoid factor positivity in study subjects

RHEUMATOID FACTOR	CASES NUMBER	PERCENTAGE
POSITIVE	33	79.5%
NEGATIVE	9	20.5%
TOTAL	42	

Out of the 42 study patients 33 were RA FACTOR positive.

TABLE 5B

COMPARISON OF RA FACTOR POSITIVE & NEGATIVE CASES

GROUP	Total No of subjects	LDL / HDL MEAN	Total Chol / HDL MEAN	C I M T (mm) MEAN	Mean Duration of illness (yrs)	DAS SCORE MEAN
RA factor +ve	33	3.29	5.52	7.0	5.15	4.32
RA factor -ve	9	3.19	5.32	6.7	3.95	3.98
P VALUE	-----	0.34 (NOT SIGNIFICANT)	O.29 (NOT SIGNIFICANT)	0.083 (NOT SIGNIFICANT)	0.22 (NOT SIGNIFICANT)	0.067 (NOT SIGNIFICANT)

There was **no significant difference** in LDL/HDL RATIO, Total Cholesterol / HDL ratio, DAS SCORE & CIMT values between rheumatoid factor positive and rheumatoid factor negative patients.

DISCUSSION

Studies of myocardial infarction and other CV events in patients with rheumatoid arthritis (RA) have consistently found that their incidence is at least twice as high as in controls without RA.[82,83]

The first reports of ischemic heart disease morbidity in comparison with the general population were presented in 2001, when Del Rincón[107] et al. showed that patients with rheumatoid arthritis suffered an almost four-fold increased risk of cardiovascular events, incidence rate ratio 3.96 (95% confidence interval 1.86, 8.43) . They used an outcome definition including cerebrovascular disease, as well as ischemic heart disease, but in 2003 Solomon[108] et al. presented data from the Nurses Health Study, suggesting that there indeed was an increased risk of ischemic heart disease (in this case, myocardial infarction) in the rheumatoid arthritis population.

An important metabolic feature of RA is the catabolic state leading to loss of body cell mass due to a accelerated loss of skeletal muscle (Walsmith[109] et al 2004). This is known as rheumatoid cachexia and important mediators are TNFα and other proinflammatory enzymes. These mediators are also associated with low TC and HDL-C levels (Kotler[110] 2000), and as a higher disease activity in RA is accompanied

with a higher TNF level this might explain the relationship between disease activity and lipid levels.

Our cross-sectional study was conducted in 42 patients with RA in Govt. Rajaji Hospital, Madurai. Lipid profiles and CIMT of all patients were compared with a control group matched for sex, age, and body mass index. Each patient was assessed through a self-reported questionnaire, structured interview and physical examination. Blood samples were obtained for routine biochemistry, lipid profile and haematological tests.

The sex distribution in this study, predominantly affects females in the ratio of 3.5:1. According to Harrison 17th edition, API text book of medicine, the females are affected 3 times more than males. In this study males are 22% and females are 78%. In Doran MF &Ponal et al study, males are 26.9% and females are 73.1%[86].

The mean age in our study is 40.2years. Most number of cases is in between 31- 50years (69%). In a study conducted by Mary.J.Roman et al, average age of patients was 35 years. The average age of patients in our study was comparable to that of other studies.[87]

In this study, average duration of rheumatoid arthritis is 5.2 ± 3.5 years. Most number of patients had a duration between between 3 -7 years of age (57%). In a study by Anna Sodergren et al[88], the mean age of

study group were 37.6 years (Range 18-66) and the mean duration of rheumatoid arthritis was 3.6 years at the time of conducting CIMT testing.

In our study RF is positive in 80% of cases. There is no significant difference in LDL/HDL RATIO, Total Cholesterol / HDL ratio, Das Score & CIMT values between rheumatoid factor positive and rheumatoid factor negative patients. The reference analysis as suggested by Jane E. Salmon & Dr. Targher[90] et al also showed no association between autoantibodies (rheumatoid factor or anti-CCP antibodies) and the presence of carotid atherosclerosis in their patients. Carotid plaque was detected in 49% of patients with positive results for rheumatoid factor and in 46% of patients with negative results for rheumatoid factor ($P = 0.78$), as well as in 42% of patients with anti-CCP antibodies and 44% of those without anti-CCP antibodies ($P = 0.84$). Furthermore, although titers of anti-CCP antibodies may predict radiographic outcome and disease severity in rheumatoid arthritis, they did not predict carotid atherosclerosis.

In our study average DAS 28 score is 4.68±0.74;most of the patients were having moderate severity (score between 3.2- 5.1). 21 out of 45 patients (48%) were having moderate disease activity. 38% of patients had severe disease activity according to DAS 28. Carotti et al[89] in their study reported 14.6% patients had mild disease, 48.4% had moderate DAS score and 45.5 % of patients had severe disease activity. In

our study there is no relation between DAS score and atherogenic index or CIMT values. In a study by Anna Sodergren et al[88], there was no relation between the disease activity measurements, that is, DAS28 & HAQ and the ultrasound measurements in the RA patients at the time of the baseline investigation. In a study by Carotti et al[89] no significant correlation was found for CIMT with clinical and laboratory parameters reflecting disease activity.

Out of the total 42 study patients, 37 (88.1%) are CRP positive. The LDL / HDL ratio is significantly higher in CRP positive patients. The Total Cholesterol / HDL ratio is significantly higher in CRP positive patients.HDL cholesterol values are significantly lower in CRP positive patients. There was no significant difference in Total Cholesterol, Triglyceride, Non-HDL , LDL Cholesterol & CIMT values between CRP positive and negative patients. In another study, Dessein P.H[92] et al showed that high C-reactive protein (CRP) concentrations were associated with insulin resistance and hypertension, while insulin resistance was a statistical predictor of low HDL cholesterol and high triglycerides.

One of the first controlled studies reporting on apolipoprotein levels in RA was performed in 42 untreated patients (mean disease duration 27 months) and 42 age- and sex-matched controls (Park et al 1999)[93]. The investigators found significantly lower levels of apolipoprotein A1 and HDL-C in patients than in controls and significantly higher levels

Lp(a) (27.1 vs 18.0 mg/dL, respectively). The ratios of apo B/apo A1, total cholesterol/HDL-cholesterol were significantly higher in patients than in controls (0.82 vs 0.67, 4.4 vs 3.4, respectively). CRP levels had an inverse correlation with apolipoprotein A1 and HDL-C indicating an adverse effect of disease activity on lipid profile. Douglas White[92] et al showed in their study that elevated ESR is associated with statistically significant alterations in HDL and LDL cholesterol levels, but this is not the case for elevated CRP where a relationship was only seen with reduced HDL levels.

In our study, the Triglyceride level & VLDL level cholesterol values are significantly higher in RA patients.($p<0.05$) . In our study HDL cholesterol values are significantly lower in RA patients. ($p < 0.0001$). In our study rheumatoid arthritis patients showed, on average, 1% higher total cholesterol ($p>0.05$), 18% lower HDL ($p<0.05$) & 27% higher triglyceride than matched controls ($p\leq0.05$). Nineteen RA patients had an elevated triglyceride level (>150) .

In Dijkmans B.A.C.[95] et al's study on dyslipidemia in Rheumatoid arthritis, blood samples of patients who later developed rheumatoid arthritis showed, on average, 4% higher total cholesterol, 9% lower HDL, 17% higher triglyceride and 6% higher apo B levels than matched controls ($p\leq0.05$).

Adrienne Davis et al[87] compared patients who had RA without carotid plaque & those with plaque and found that the latter were older at the time of the study; were older at onset of disease; had higher serum total cholesterol, low density lipoprotein cholesterol, and baseline homocysteine levels and higher systolic blood pressure; and were more often hypertensive. Most of the patients who participated in our study were taking steroids. Corticosteroids can contribute to a type 2b hyperlipidaemia. The triglyceride level , LDL and HDL values may often rise with prednisolone treatment.[10] However several other studies have been unable to demonstrate any association between cardiovascular mortality and the use of corticosteroids. A recent study reported a small or no increase in TC levels during long-term administration of corticosteroids [16.]

In our study, the LDL / HDL ratio is significantly higher in RA patients. The Total Cholesterol / HDL ratio is also significantly higher in RA patients. George Steiner[97] et al showed that Early RA patients exhibited mild higher baseline serum levels of TC, LDL-C, nonHDL-C, triglycerides and apoB. Importantly, the serum HDL-C and apoA-I levels were significantly lower compared to controls. As a consequence the atherogenic ratio of TC/HDL-C as well as that of LDL-C/HDL-C was significantly higher in ERA patients compared to controls.

In our study total cholesterol and LDL cholesterol is slightly higher in rheumatoid arthritis patients, but it did not attain statistical significance. Non – HDL cholesterol values were significantly higher in RA patients. Low high-density lipoprotein cholesterol (HDL-C<40) was seen in 53.8% of (23/42) patients. These results were comparable to the results obtained in a study conducted by V. Hadda[101] et al in which Low high-density lipoprotein cholesterol (HDL-C) was the commonest abnormality seen in 36.1% of (34/96) patients. Disease activity scores (DAS-28) were measured at baseline and on a follow-up visit after 3 months and they were 4.9 (1.02) and 4.4 (0.9), respectively (P = 0.003). With a decline in disease activity, a rising trend was observed for all lipids, statistically significant only for HDL.

Athanasios N Georgiadis[99] et al showed that RA patients exhibited higher serum levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and triglycerides, whereas their serum high-density lipoprotein cholesterol (HDL-C) levels were significantly lower compared to controls. As a consequence, the atherogenic ratio of TC/HDL-C as well as that of LDL-C/HDL-C was significantly higher in ERA patients compared to controls. After treatment, a significant reduction of the atherogenic ratio of TC/HDL-C as well as that of LDL-C/ HDL-C was observed, a phenomenon primarily due to the increase of serum HDL-C

levels. These changes were inversely correlated with laboratory changes, especially CRP and ESR.

In a similar analysis elsewhere, Dijkmans[95] et al showed in his study that RA patients exhibited higher serum levels of total cholesterol, LDL cholesterol and triglycerides, whereas their serum HDL cholesterol levels were significantly lower compared to controls. After treatment, a significant reduction of the atherogenic ratio of total cholesterol / HDL cholesterol as well as that of LDL cholesterol / HDL cholesterol was observed, a phenomenon primarily due to the increase of serum HDL cholesterol levels.

Some of the studies also report an apparent reduction in total cholesterol. This apparent reduction of total cholesterol may result from reduced synthesis, increased clearance via the scavenger receptor pathway or increased oxidation triggered by the inflammatory process. Alternatively the presence of circulating autoantibodies to VLDL and LDL in active RA may be responsible. These may also have pre-atherogenic effects on the vascular wall by forming immune complexes.[98]

Lakatos J, Hárságyi A[94] et al in their study measured the levels of total cholesterol, HDL, low density (LDL) cholesterol, and triglycerides in sera of patients with rheumatoid arthritis and in healthy controls. In patients with rheumatoid arthritis (26 men and 103 women), the

HDL cholesterol and triglycerides were lower (p less than 0.001) compared to the values observed in controls (625 men and 749 women). Similar patterns were seen when results of age and sex matched controls were compared to the results of patients suffering from rheumatoid arthritis.

A PubMed literature search was undertaken for studies published between 1990 and May 2007, using the search terms "rheumatoid arthritis" AND "lipid" OR "lipoprotein," and including all relevant drug treatment terms for glucocorticoids, disease-modifying antirheumatic drugs, and biologics. The results showed that patients with RA face an increased risk of developing premature cardiovascular disease and limited ability to modify risk factors, eg, through exercise. RA is associated with an abnormal lipoprotein pattern, principally low levels of high density lipoprotein (HDL) cholesterol. Most treatments for RA tend to improve the atherogenic index (total/HDL cholesterol ratio), with more evidence for biologics in this regard. The improvement in the lipoprotein profile in RA appears to be associated with suppression of inflammation.

The CIMT more than upper limit was seen in (13/42) RA patients (30.9%) in our study. Only 4 controls (10%) had CIMT above the upper limit. The upper limit of CIMT in our study was 0.72 cms. Values of mean CCA IMT above mean + 2 SD of the control group were

defined as abnormal IMT. This Criteria was taken from the study mentioned by Sundeep grover etal[100] . In our study, of the 13 RA patients with CIMT > 7.2mm , SIX patients had LDL/HDL > 4 and SEVEN patients had TOTAL CHO/HDL > 5, and ELEVEN (85%) patients had HDL level <40 mg/dl.

Indians are also at increased risk of developing early and severe atherosclerotic coronary artery disease. Sundeep Grover[100]etal , Department of Immunology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow conducted a study in which Common carotid IMT (CCA IMT) was measured at the level of carotid bifurcation along with fasting lipid profile in 57 RA patients and 45 age and sex matched controls. Nineteen RA patients (33.3%) and 2 controls (4.44%) had abnormal IMT values. RA patients had significantly increased mean CCA IMT (0.558 ± 0.137 mm) as compared to controls (0.416 ± 0.002 mm; $p < 0.0001$). Age ≥ 42 years, duration of disease ≥ 6 years, and tender joint count ≥ 5 predicted increased risk of having abnormal CCA IMT in a logistic regression analysis.

Carotti M[89] et al showed in their study that the carotid IMT were significantly higher (p=0.0009) in RA patients (0.83 +/- 0.23) compared with controls (0.66 +/- 0.22). In RA patients common carotid IMT was significantly correlated with serum total cholesterol (p=0.0008), low-density lipoprotein cholesterol (p=0.006), triglycerides (p=0.042), age

(p=0.031) and disease duration (p=0.019). No significant correlation was found with clinical and laboratory parameters reflecting disease activity.

In our study, the CIMT is significantly higher in RA patients. (0.68 ± 0.08 vs 0.58 ± 0.07, p value = 0.03). In a similar study conducted by Ozgur Ciftcia et al, thirty RA patients (22 women; mean age 43.7 ± 9.0) and 52 healthy volunteers (38 women; mean age 45.3 ± 5.4) were included and in carotid Doppler study, cIMT values were significantly increased in RA patients.(0.6 ± 0.1 vs. 0.5 ± 0.1, $P < 0.05$).

In our study, CIMT was measured by ultrasonography in 42 non-diabetic, normotensive, RA patients and 40 matched healthy controls [age 40.2 (6.9) *vs* 41.7 (8.1) years]. Gorica G. Ristić et al did a study to evaluate the extent of subclinical atherosclerosis in patients with RA and low cardiovascular risk by measuring intima-media thickness (IMT) of the carotid arteries and to determine factors associated with increased IMT. CIMT was measured by ultrasonography in 42 non-diabetic, normotensive, female RA patients and 32 matched healthy controls [age 45.3 (10.0) *vs* 45.2 (9.8) years] at common carotid arteries (CCAs), carotid bifurcation (BF) and internal carotid arteries (ICAs), bilaterally. Mean and maximal (max) IMTs were calculated from three measurements at each site.

RA patients had increased IMT (mm) in comparison with controls [CCA_{max}: 0.764 (0.148) *vs* 0.703 (0.100); CCA_{mean}: 0.671 (0.119) *vs* 0.621 (0.085); BF_{max}: 1.055 (0.184) *vs* 0.941 (0.161); BF_{mean}: 0.889 (0.168) *vs* 0.804 (0.124); ICA_{max}: 0.683 (0.108) *vs* 0.613 (0.093); ICA_{mean}: 0.577 (0.101) *vs* 0.535 (0.076)]. Parameters associated with IMT in RA patients were (correlation at *x*/6 measurement sites): age (6/6), BMI (2/6), smoking (2/6), RF concentration (2/6), sedimentation rate (1/6) and duration of MTX + chloroquine therapy (4/6; inverse correlation).

Multivariate regression analysis revealed that RA is an independent risk factor for increased IMT. Factors correlating with IMT in the controls were: age (6/6), BMI (3/6), total cholesterol (5/6), low-density lipoprotein cholesterol (3/6), total/high-density lipoprotein cholesterol (2/6), triglycerides (1/6) and glycaemia (4/6).

Alper M. van Sijl et al conducted a Meta – Analysis in which a systematic literature search and meta-analysis were performed to evaluate cIMT difference between RA and controls. From 22 studies, cIMT data were available from 1384 RA patients and 1147 controls. In 17 of the studies, RA patients had a statistically significantly greater cIMT. The overall mean cIMT difference was 0.09 mm (95%CI: 0.07-0.11 mm).

In our study, RA patients with more than 5 years disease duration have a higher atherogenic index and higher CIMT than those with less than 5 years of illness. cIMT had previously been found to be increased in patients with long standing RA as shown by del Rincon[104] et al. He showed that those with long duration (> 20 years) had a higher cIMT compared with patients of the same age but shorter disease duration (< 7 years).

Pascal N. Tyrrell[105] et al recently did a systematic review and meta-analysis to examine whether rheumatic disease is associated with an increased CIMT (increasingly used as a surrogate marker for atherosclerosis) when compared with healthy control subjects. A total of 68 controlled comparisons from 60 different studies were reviewed: 25 (37%) on RA, 24 (35%) on SLE, 6 (9%) on systemic sclerosis, and 13 (19%) on other rheumatic diseases. The estimated summary effect size between control and study subject CIMT measurement comparisons, with preexisting cardiovascular disease excluded, was 0.64 (95% CI, 0.46 to 0.82). This represented an overall absolute mean difference of 0.06 mm (95% CI, 0.05 to 0.06 mm). Preexisting cardiovascular disease, rheumatic disease type, and disease duration contributed to heterogeneity.

Carlos Gonzalez-Juanatey[106] et al did a study to establish whether carotid intima-media wall thickness (IMT) may be a good predictor for the development of cardiovascular (CV) events in patients with rheumatoid arthritis (RA). A series of 47 RA patients who at the time of recruitment did not have traditional CV risk factors or CV disease were assessed by carotid ultrasonography. Carotid IMT was measured in the right CCA. Then, a prospective assessment of the CV outcome was performed over a 5-year period.

Carotid IMT was greater in RA patients who over the extended follow-up experienced CV events (1.01 ± 0.16 mm), compared with the remaining RA patients who did not have CV complications (0.74 ± 0.12 mm) ($P < 0.001$). None of the patients with carotid IMT less than 0.77 mm had CV events. However, 6 of the 10 patients with carotid IMT greater than 0.91 mm experienced CV events (p value for the trend <0.001). Carotid IMT yielded a high predictive power for the development of CV events over the 5-year follow-up period. The results from this study support the use of carotid ultrasonography as a predictor of CV events in RA.

LIMITATIONS OF THE STUDY

Most of the patients who participated in the study were on steroids and a few were also on DMARD/immunosuppressants. The dosage and frequency of intake of drugs were highly variable among the participants. This may have influenced the values in the study as their modifying effect on lipid profile and CIMT were not taken into account during the period of study.

SUMMARY

1. Cardiovascular manifestations are frequent in rheumatoid arthritis (RA) and significantly contribute to morbidity and mortality in this disorder. Premature atherosclerosis is responsible for these complications, as supported by autopsy studies.

2. A total of **42** [FEMALE (F)-33 ; MALE (M)-9] RA patients participated in our study.

3. There is **no significant difference** in Total Cholesterol and LDL values between RA patients and the control population.

4. In our study, (**19/42) RA** patients had an **elevated triglyceride** level.

5. As many as **23 RA** patients had a **low HDL level** (<40).

6. Among the control group - [TOTAL – 40 (M-10/F-30) controls] - only 5 had an elevated triglyceride level & only 9 had a low HDL level.

7. Among RA group , **24** patients(**57%**) had **LDL / HDL ratio >3** when compared to only 5% in the control group.

8. **Ten(25%)** RA patients had LDL/HDL ratio > 4.

9. Interestingly**, 21** RA patients **(50%)** had **Total Chol/ HDL ratio> 5** while only 5% of control population had such an **atherogenic profile**.

10. Thirteen (31%) RA patients had **CIMT > 7.2 mm** while only 4 in the control group had elevated values.

11. There is **no significant difference** between rheumatoid factor positive and rheumatoid factor negative patients.
12. The mean duration of illness in the study is **5.1 years**.
13. CIMT is **higher** in all age groups in RA patients when compared to control population.
14. The **CIMT** is **significantly** high in RA patients.
15. The **LDL / HDL** ratio is **significantly** high in RA patients.
16. The **Total Cholesterol / HDL** ratio is also **significantly** higher in RA patients.
17. There is **no relation** between DAS score and atherogenic index or CIMT values.
18. RA patients with more than 5 years disease duration have a higher atherogenic index and higher CIMT.
19. The HDL cholesterol values are significantly low and the TOTAL CHO/HDL & LDL/HDL ratios are significantly high in RA patients.
20. The **LDL / HDL** ratio & The **Total Cholesterol / HDL** ratio are significantly **high in CRP POSITIVE** patients.
21. **HDL** cholesterol values are significantly **low in CRP positive** patients.
22. RA is an independent risk factor for increased CIMT.

CONCLUSION

- Forty two RA patients attending Rheumatology clinic, Govt. Rajaji Hospital, Madurai, and 40 controls who satisfied the inclusion and exclusion criteria were selected for the study.
- RA patients have an atherogenic lipid profile and a significant increase in Carotid Intima Media Thickness.
- There is no significant difference in Total Cholesterol and LDL values between RA patients and the control population.
- The Triglyceride level , VLDL level & non – HDL cholesterol level is **significantly high** in RA patients.
- HDL cholesterol values are **significantly low** in RA patients.
- The **LDL/ HDL** ratio is **significantly** higher in RA patients.
- The **Total Cholesterol / HDL** ratio is also **significantly** high in RA patients.
- RA patients with more than 5 years disease duration have a higher atherogenic index and higher CIMT values.
- There is **no relation** between DAS score and atherogenic index or CIMT values.
- There is **no significant difference** between rheumatoid factor positive and rheumatoid factor negative patients.

- The **LDL / HDL** ratio & The **Total Cholesterol / HDL** ratio is significantly **higher in CRP POSITIVE** patients. **HDL** cholesterol values are significantly **low in CRP positive** patients.
- The **CIMT** is **significantly** high in RA patients compared to controls.
- Thirteen (31%) RA patients had **abnormal CIMT.**
- RA is an **independent risk factor** for increased CIMT.
- Lipid levels should be monitored and managed in patients with RA to minimize the long-term risk of cardiovascular disease. More research is needed to quantify the relationship between systemic inflammation and lipoprotein levels and to determine the impact of specific lipoprotein particles, eg, small dense low-density lipoprotein and sub fractions of HDL on long-term risk. Control of inflammation may have an effect on modifying cardiovascular risk.

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PROFORMA

NAME : AGE: SEX:

PHONE NO : OP NO:

ADDRESS:

HISTORY:

Arthritis :
Nodules :
Raynaud's phenomenon :
Sicca symptoms :
Syncope /chest pain /palpitation
Wheeze / dyspnoea / weakness.

Arthritis	+ / -		+ -
MCP			
PIP			
DIP			
Wrist		Morning stiffness	
Elbow		Nodules	
Shoulder		Raynaud's	
TM		Eye—Red ,,Dry	
SC			
		Rash	
Hip			
Knee		Ulcers	
Ankle		Gangrene	
ST			
		Numbness/ paraesthesia	
MT			
Spine		Nail fold infarct	

Duration of illness

DAS 28 SCORE

Past history

TB, Hepatitis, DM, CAD, HT, Hypothyroidism , IHD.

Personal history

Smoking , CAD, use of ocp, steroids

Occupation

Family history:

DM/HT/CAD/Hypercholesterolemia.

General examination

Pallor Icterus Cyanosis Clubbing Lymphadenopathy Oedema

PR BP BMI

Markers of atherosclerosis

CAROTID BRUIT + -

Systemic examination:

RS: CVS:

ABDOMEN: CNS:

INVESTIGATIONS:

Hematology: Hb TC DC

Sugar Urea Creatinine TSH LFT

LIPIDS Total Cholesterol TGL LDL HDL VLDL

Tot Cho / HDL LDL/HDL

ESR ECG RF CRP X-RAYS

CAROTID DOPPLER STUDY

CIMT (MM) : RT : LT : MEAN :

Treatment History

Steroids

Methotrexate

Hydroxy chloroquine

Other immune agents

ABBREVIATIONS AND ACRONYMS

- CIMT - Carotid Intima Media Thickness
- BP - Blood Pressure
- M - Male
- F - Female
- TC - Total cholesterol
- CRP - C reactive protein
- ESR - Erythrocyte sedimentation rate
- RA - Rheumatoid arthritis
- RF - Rheumatoid factor
- DAS - Disease activity scale
- BMI - Body mass index
- TGL - Triglyceride
- VLDL - Very low density lipoprotein
- LDL - Low density lipoprotein
- HDL - High density lipoprotein
- TSH - Thyroid stimulating hormone
- CAD - Coronary artery disease

MASTER CHART ABBREVIATIONS

Age	AGE
Sex	SEX
DUR	DURATION OF ILLNESS IN YEARS
PRV	PREVIOUS TREATMENT
RA f	RHEUMATOID FACTOR
CRP	C-Reactive Protein
ESR	Erythrocyte Sedimentation Rate
Das28	Disease Activity Scale
TGL	TRIGLYCERIDE LEVEL
VLDL	VLDL CHOLESTEROL
LDL	LDL CHOLESTEROL
HDL	HDL CHOLESTEROL
TOT.C	TOTAL CHOLESTEROL
NO.HC	NON HDL CHOLESTEROL
LD/HD	LDL/HDL RATIO
TC/HD	TOTAL CHOLESTEROL/HDLCHOLESTEROL
RBS	Random Blood Sugar
HB	Hemoglobin
TSH	Thyroid stimulating hormone
Urea	UREA
CR	CREATININE
BP	BLOOD PRESSURE
BMI	Body Mass Index
CIMT	Carotid Intima Media Thickness
CrB	Carotid Bruit
ECG	Electrocardiogram
NEG	NEGATIVE
POS	POSITIVE

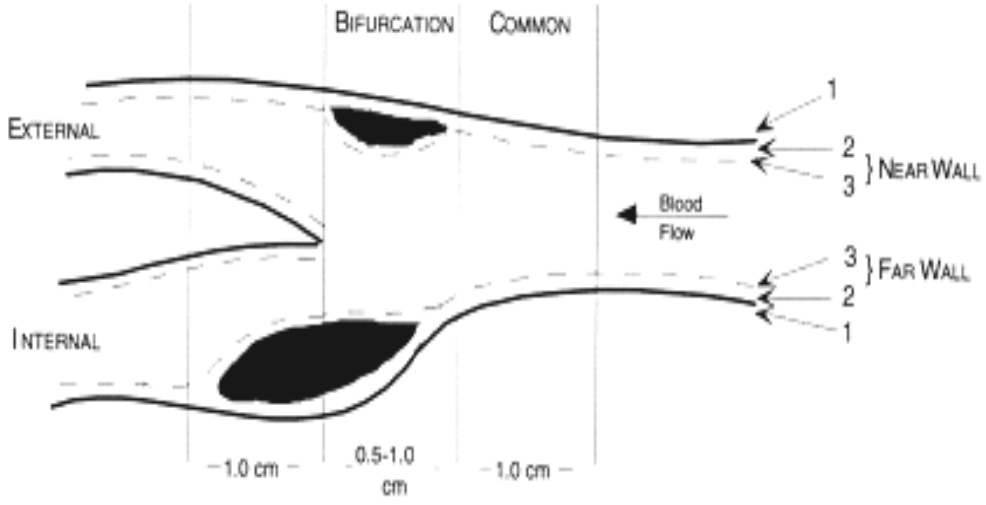


Figure 1- showing how to measure CIMT

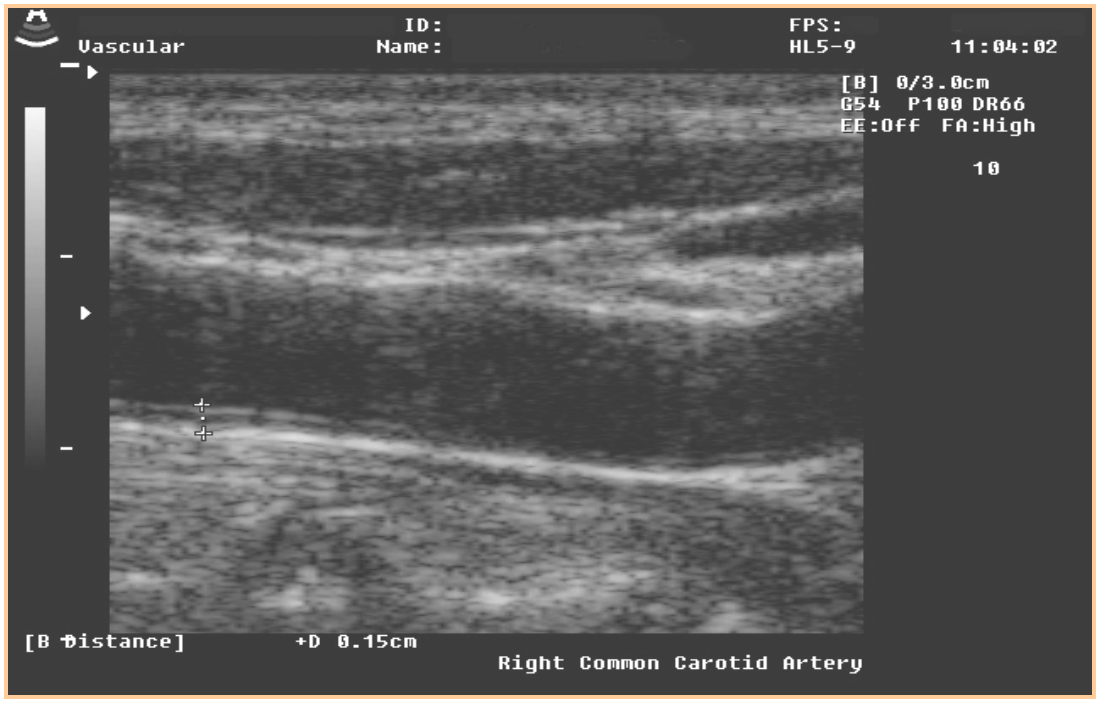


Figure 2 MEASURING INTIMA MEDIA THICKNESS IN RIGHT CCA

FIG 1A- **AGE GROUP DISTRIBUTION IN STUDY AND CONTROL GROUP**

FIGURE 1B **SEX DISTRIBUTION IN BOTH GROUPS**

FIGURE 1C **DURATION OF ILLNESS**

FIGURE 1G

DAS SCORE DISTRIBUTION AMONG STUDY POPULATION

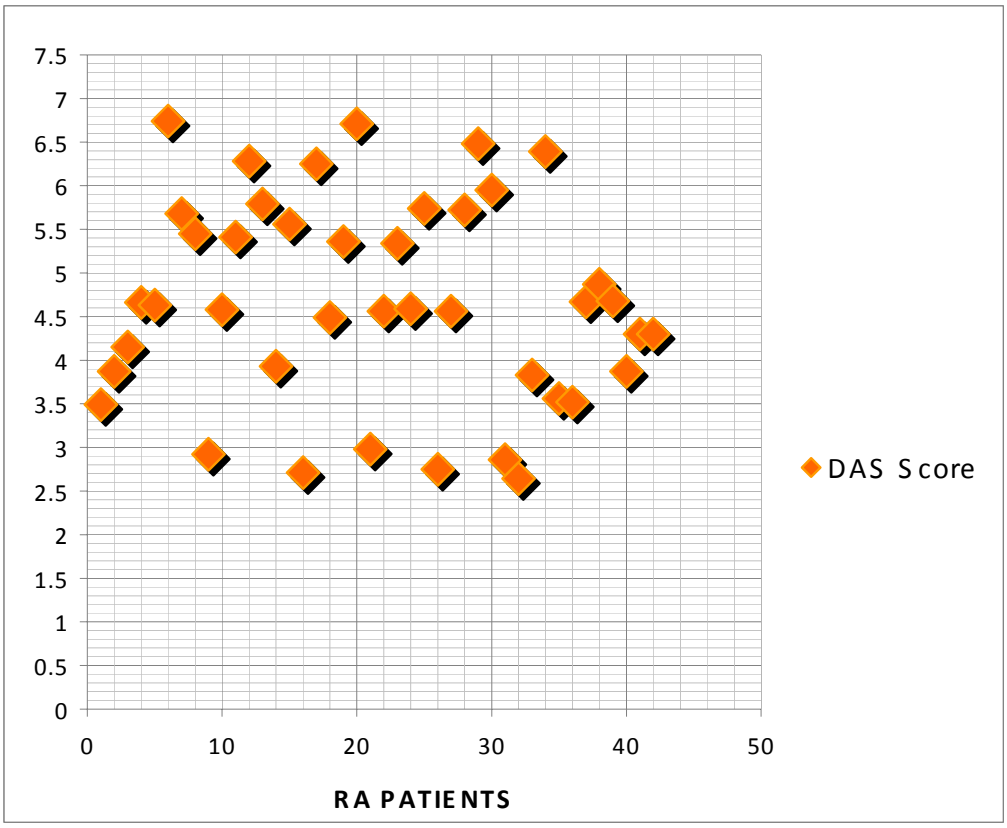


FIGURE 2A **BMI & LIPID PROFILE IN STUDY GROUP AND CONTROL GROUP**

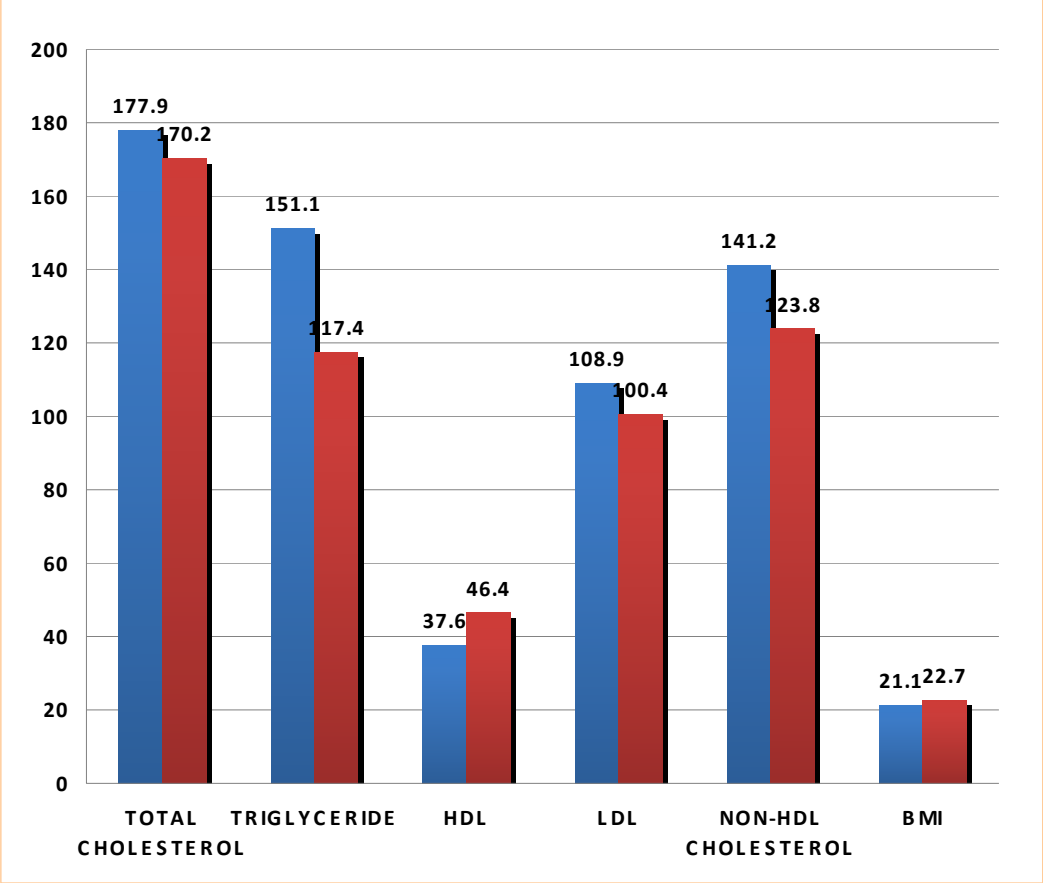


FIGURE 2C-

CAROTID INTIMA MEDIA THICKNESS IN STUDY & CONTROL GROUP

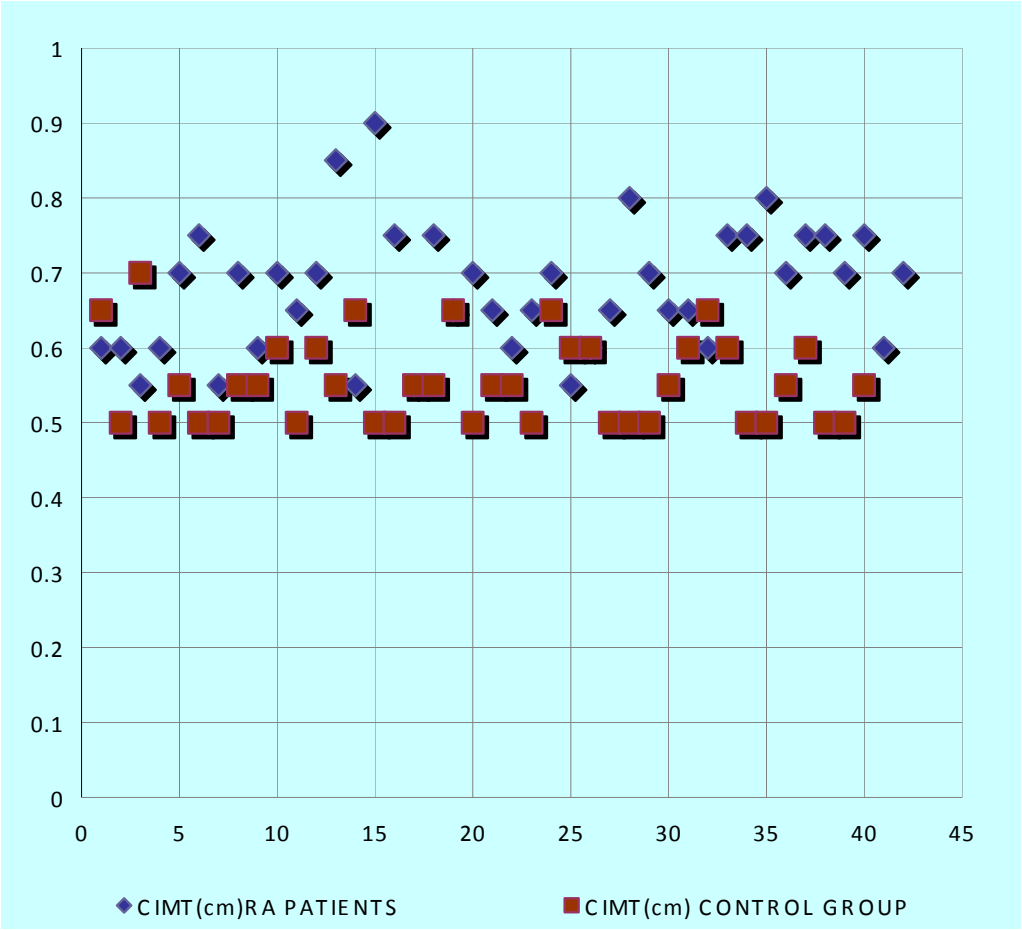


FIGURE 2B -**CIMT AND ATHEROGENIC INDEX IN STUDY GROUP & CONTROL GROUP**

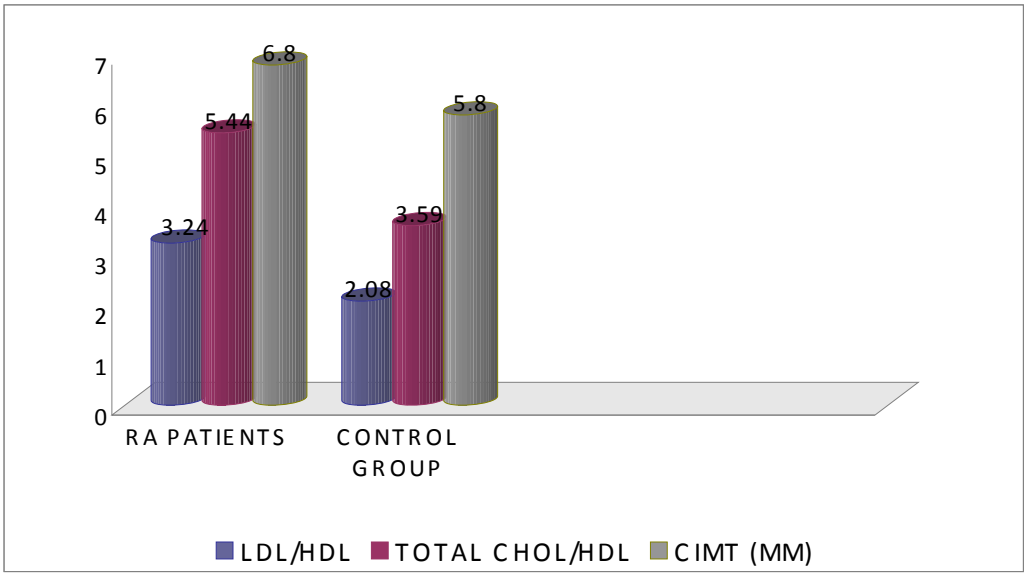


FIGURE 3A

AGE & CAROTID INTIMA MEDIA THICKNESS IN STUDY & CONTROLS

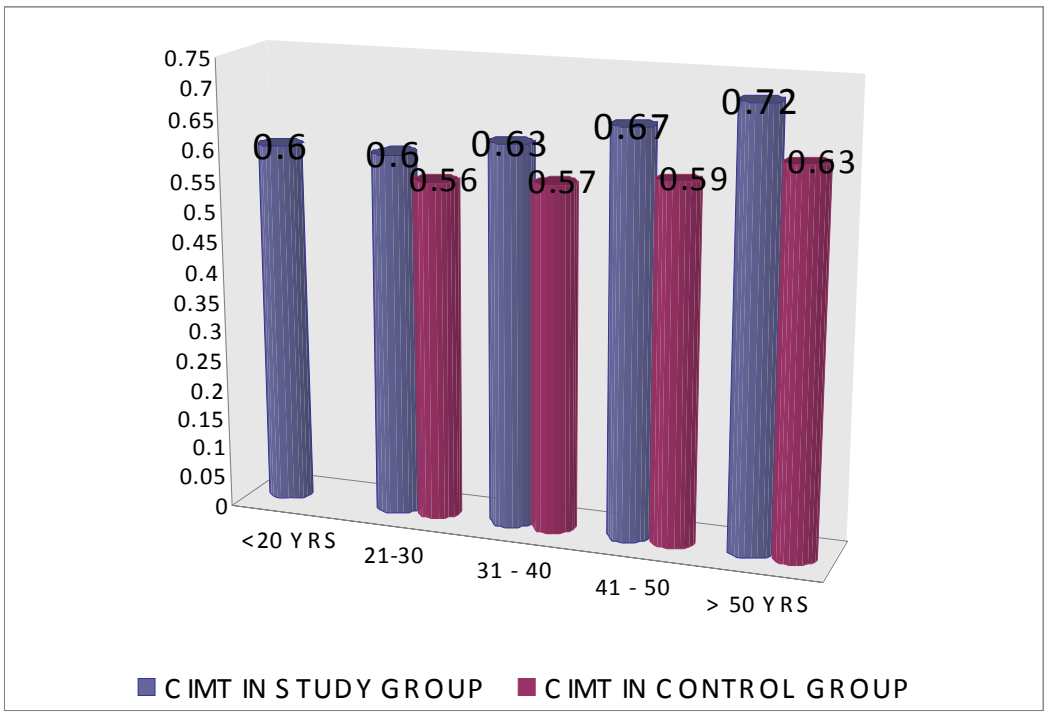
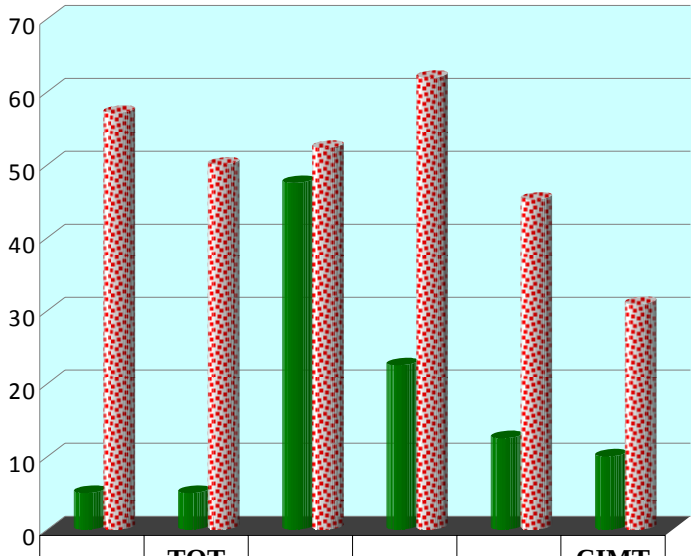


FIG 3 B

CIMT , LIPID PROFILE & ATHEROGENIC INDEX IN STUDY GROUP & CONTROL GROUP



	LDL/ HDL>3	TOT CHO/ HDL>5	LDL> 100	HDL<40	TGL>150	CIMT >7.2 mm
CONTROLS(%WITH SIGNIFICANT CHANGE)	**5**	**5**	**47.5**	**22.5**	**12.5**	**10**
RA PATIENTS (% WITH SIGNIFICANT CHANGE)	**57.1**	**50**	**52.3**	**61.9**	**45.2**	**30.9**

FIGURE 3C - **ATHEROGENIC INDEX AND CAROTID INTIMA MEDIAL THICKNESS IN RELATION TO DAS SCORE**

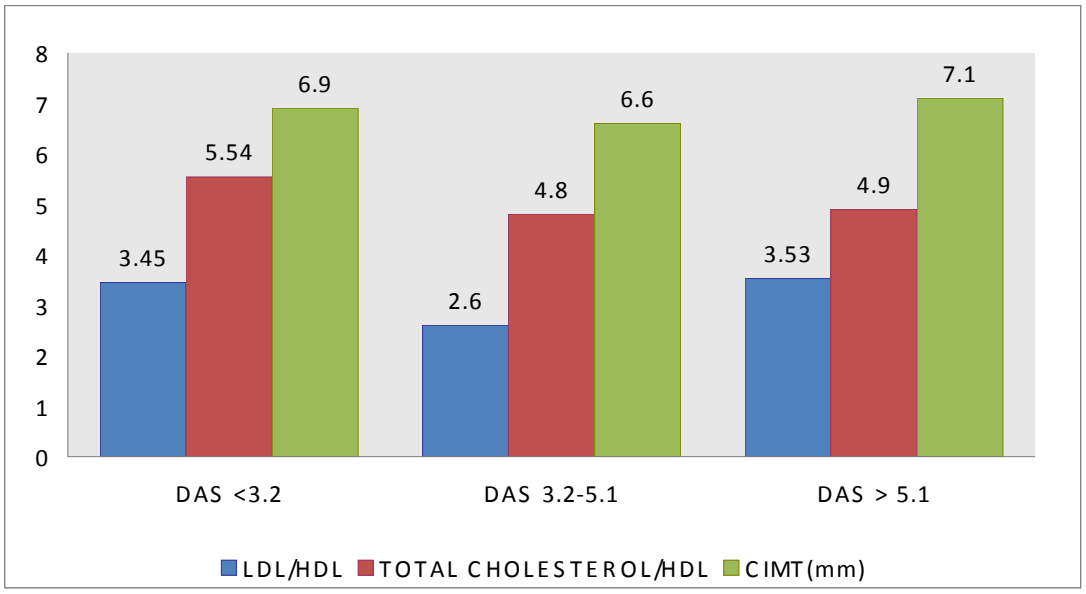


FIGURE 3D **DISEASE DURATION AND ATHEROGENIC INDEX AND CIMT**

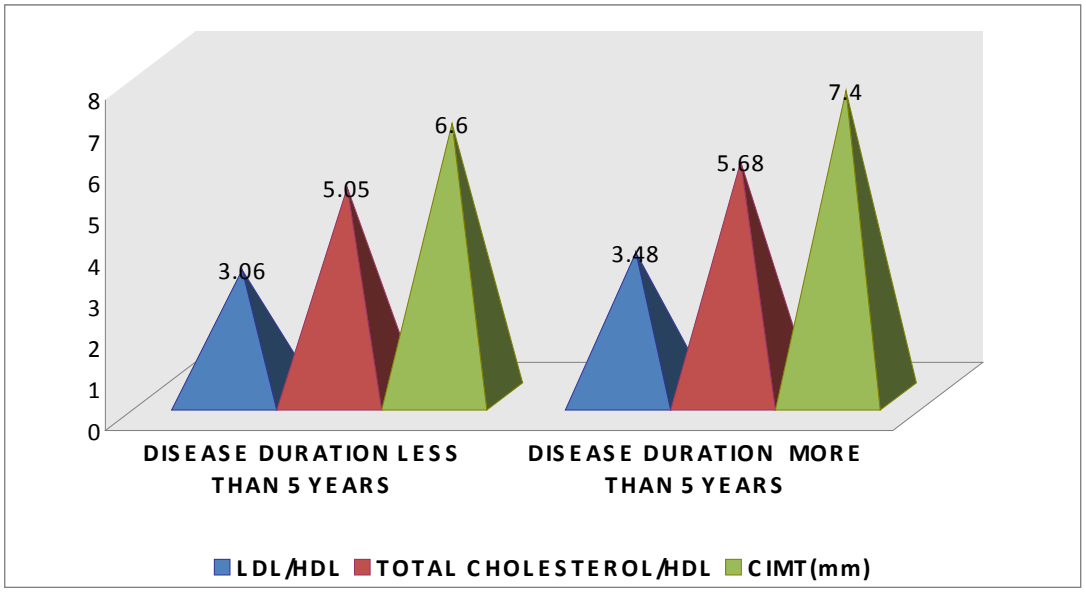


FIG4A –

COMPARISON BETWEEN CRP POSITIVE & NEGATIVE CASES

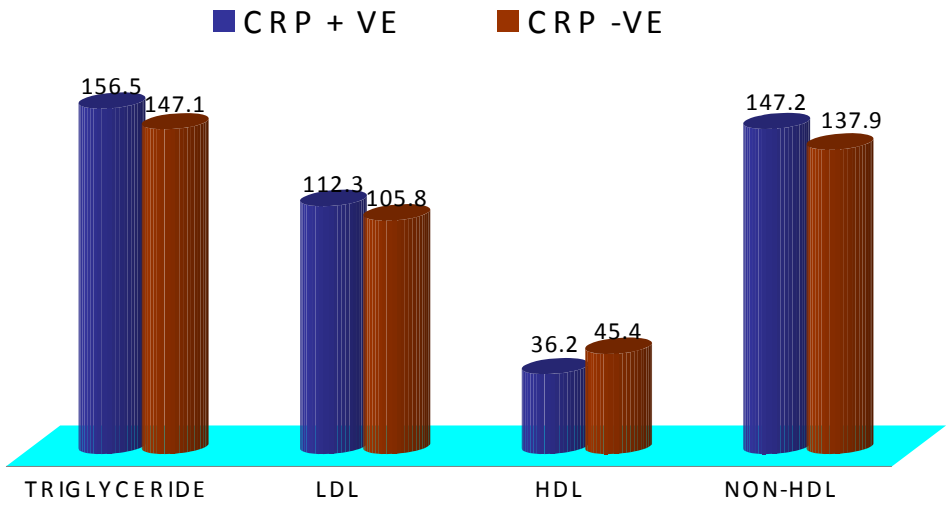
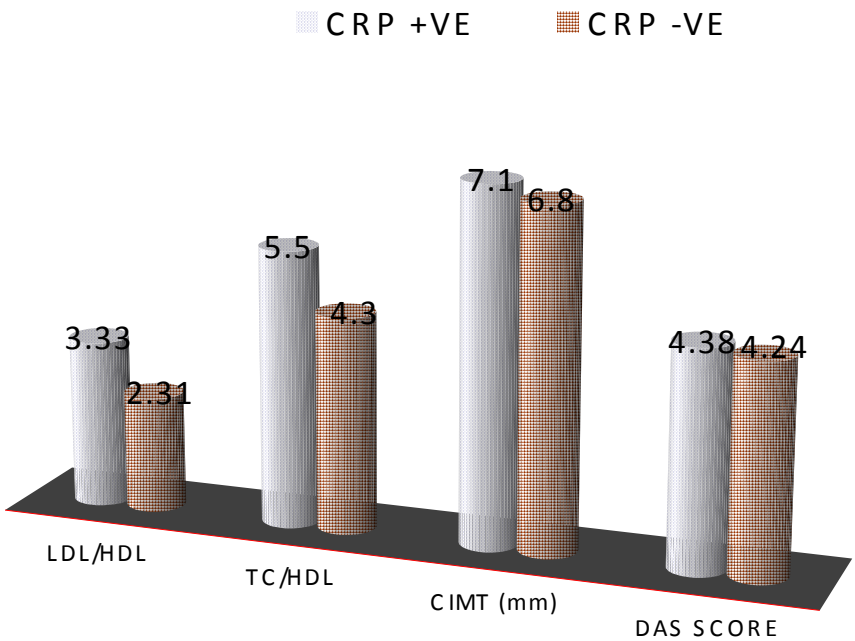


FIGURE 4 B -

COMPARISON BETWEEN CRP POSITIVE AND CRP NEGATIVE CASES



COMPARISON OF RHEUMATOID FACTOR POSITIVE & NEGATIVE CASES